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(54) Title: NOVEL COMPLEXES OF FATTY ACID ESTERS OF POLYHYDROXYALKANES AND PYRIDINE CARBOXY DERIVATIVES

(57) Abstract: The present invention relates to novel combinations of fatty acid derivatives and pyridine carboxy derivatives, including fatty acid esters with glycerol and 3-carboxy pyridine derivatives such as niacinamide. Such combinations have surprisingly shown antiviral and anti-microbial activity and the use for the treatment of inflammatory conditions and infections is disclosed herein.

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## **NOVEL COMPLEXES OF FATTY ACID ESTERS OF POLYHYDROXYALKANES AND PYRIDINE CARBOXY DERIVATIVES**

### **FIELD OF THE INVENTION**

The present invention relates to chemical complexes and pharmaceutical compositions comprising a combination of a fatty acid ester of a polyhydroxyalkane and a pyridine carboxy derivative. Their therapeutic application as agents for suppression of hypersensitivity and inflammatory reactions with additional anti-microbial effects, such as bactericidal or fungicidal actions, is disclosed herein.

### **10 BACKGROUND OF THE INVENTION**

Hypersensitivity is defined as a state of altered reactivity in which the body reacts with an exaggerated immune response to a substance (antigen). Hypersensitivity may be caused by exogenous or endogenous antigens. Hypersensitivity reactions underlie a large number of diseases. Among these, allergic and autoimmune conditions are of great importance. A classification of hypersensitivity diseases is given in the textbook Clinical Medicine (Kumar, P. and Clark, M.: "Clinical Medicine", 3rd edition, p. 147-150, 1994, Bailliere Tindall, London).

Type I hypersensitivity reactions (IgE mediated allergic reactions) are caused by allergens (specific exogenous antigens), e.g. pollen, house dust, animal dandruff, moulds, etc. Allergic diseases in which type I reactions play a significant role include asthma, eczema (atopic dermatitis), urticaria, allergic rhinitis and anaphylaxis.

Type II hypersensitivity reactions are caused by cell surface or tissue bound antibodies (IgG and IgM) and play a significant role in the pathogenesis of myasthenia gravis, Goodpasture's syndrome and Addisonian pernicious anaemia.

Type III hypersensitivity reactions (immune complex) are caused by autoantigens or exogenous antigens, such as certain bacteria, fungi and parasites. Diseases in which type III hypersensitivity reactions play a significant role include lupus erythematosus, rheumatoid arthritis and glomerulonephritis.

Type IV hypersensitivity reactions (delayed) are caused by cell or tissue bound antigens. This type of hypersensitivity plays a significant role in a number of conditions, e.g. graft-versus-host disease, leprosy, contact dermatitis and reactions due to insect bites.

Type I to type IV hypersensitivity reactions are all classically allergic reactions, which may lead to histamine release. However, hypersensitivity reactions are also those, where histamine release is triggered through the directly action of "triggering substances" with the cellular membrane. Examples of "triggering substances" are, but not limited to, toxins,  
5 food constituents and certain drugs.

A number of drug classes are available for the treatment of hypersensitivity and related inflammatory reactions.

Among these, the corticosteroids are some of the most widely used drugs. Corticosteroids  
10 primarily exert their pharmacological action by non-selectively inhibiting the function and proliferation of different classes of immune cells resulting in suppression of hypersensitivity reactions. Unfortunately, the corticosteroids are associated with a number of serious side effects, e.g. immunosuppression, osteoporosis and skin atrophy. Alternative drugs are associated with serious toxicity. There is a strong need for effective and safer alternatives  
15 to the existing antiinflammatory drugs.

Often hypersensitivity or inflammatory disease as described above is associated with or even caused by pathogenic bacteria, fungi or viruses. A number of pathogenic bacteria and fungi play an essential role in the development of a plethora of diseases, including skin  
20 diseases. For example, atopic dermatitis, which is widely considered as an inflammatory skin disorder is often associated with secondary infections, e.g. with *Staphylococcus Aureus*, thus giving rise to aggravation of the symptoms. Similarly, the facial eczematous disease seborrheic dermatitis is associated with fungal infections, typically caused by *Pityrosporum ovale*. Today, such skin diseases are often treated with corticosteroids.  
25 Antibiotics may also be applied, but today the topical application of traditional antibiotics is limited due to the risk of adverse effects and development of resistant strains of micro organisms, which can cause severe problems.

*Herpes labialis* (cold sores) is associated primarily with unpleasant inflammation and  
30 blisters occurring on the lips and face as the primary symptoms, but the cause of the disease is a viral infection with *Herpes simplex* type 1.

Similarly, *acne vulgaris* is an inflammatory disease of the sebaceous glands and hair follicles of the skin, but a primary cause of the disease is a bacterial infection with *Propionibacterium acnes*.

35 Infections are treated with antibiotics with diverse specific mechanisms of action and often associated with unpleasant adverse effects. Unfortunately antibiotics often give rise to the development of resistance. Resistant strains of bacteria, which are practically untreatable, are a growing problem due to the widespread use of antibiotics.

Obviously there is a strong need for safer antibiotics and treatments that combine antibacterial, antiviral or antifungal effects with symptom relieving antiinflammatory effects.

- 5 Niacinamide, which is also known as nicotinamide, has been found to be a potent inhibitor of poly(ADP-ribose)polymerase.
- Poly(ADP-ribose)polymerase, also known as poly(ADP-ribose)synthetase or poly(ADP-ribose)transferase is an nuclear enzyme that catalyses the posttranslational modification of nuclear proteins by covalent attachment of ADP-ribosyl moieties derived from NAD<sup>+</sup> with
- 10 an accompanying release of nicotinic acid amide. Preferred acceptor proteins are nuclear histones, whose poly-ADP-ribosylation induces local alterations in the architecture of chromatin domains.

- Inhibitors of poly(ADP-ribose)polymerase have been found to suppress hypersensitivity
- 15 reactions and inflammation. Thus, Ungerstedt et al. (Clin Exp Immunol. 2003 Jan;131(1):48-52) found that niacinamide inhibits the expression in human whole blood of the pro-inflammatory cytokines IL-1 $\beta$ , IL-6, IL-8 and TNF- $\alpha$ . This may explain some of the beneficial effects reported, e.g. in the prophylaxis of aggravation of diabetes and symptoms of osteoarthritis as elaborated by McCarthy et al (Med Hypotheses. 1999
- 20 Oct;53(4):350-60). Still niacinamide and similar pyridine carboxy derivatives are considered as mild and speculative antiinflammatory agents, which is also why they are not at present in established clinical use.

JP 964497 discloses the use of niacinamide for preventing mildew and for use as a food preservative. There is no mention of medicinal use or use as an antibiotic.

25

- Disinfecting properties of fatty acids have been acknowledged for more than a century. The use of bar soap is a practical example of this, which besides solubilization of dirt also provides a mild degree of disinfection of the skin. The acknowledgement of the preferable use of certain fatty acids or derivatives thereof for inhibition of microorganisms is
- 30 exemplified by US 4,002,775, which discloses the use of specific fatty acids and derivatives as antimicrobial agents in relation to food preservation.

- EP 465423 discloses a pharmaceutical composition for killing microorganisms containing fatty acids and monoglycerides thereof. Fatty acid esters of other glycols are not disclosed and the combination or complex formation with pyridine carboxy derivatives is not
- 35 mentioned. Therefore the relevance to the present invention is limited.

The same is the case with WO 9820872, which discloses a method for counteracting infection of the genital mucosa of a mammal by applying compositions containing C<sub>6</sub> to C<sub>18</sub> fatty acids or monoglycerides or fatty alcohol esters thereof to the genital mucosa.

US 5,231,087 discloses a method of treating certain skin diseases and tumours with esters and amides of monocarboxylic acids having 9 to 18 carbon atoms. The proposed esters include esters of a broad variety of alcohols ranging from monohydric alcohols up to esters of saccharides and polyethylene glycol, which is completely besides the scope of the present invention. Furthermore there is no disclosure of combination or complex formation with pyridine carboxy derivatives.

As recognised by the present inventor, there is a need for agents that provide combined anti-inflammatory and anti-microbial therapeutic effects in an efficient manner and without the adverse effects associated with existing medication.

### SUMMARY OF THE INVENTION

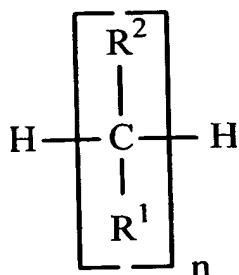
The present inventor has found that a combination of a fatty acid ester of a polyhydroxyalkane and a pyridine carboxy derivative significantly suppresses inflammatory reactions. Both of these groups of components of the complexes of the invention hold the advantage of being non-toxic and very well tolerated compared to existing antiinflammatory drugs, which are generally associated with severe and treatment limiting adverse effects. Experimental data presented in example 111 demonstrate that the surprising and powerful antiinflammatory effects of the complexes of the invention are due to a synergistic effect between the components of the complexes of the invention. At the dose giving maximal effect in a recognised mouse model of dermal inflammation the complex of the invention gave 65% more inhibition of inflammation than the sum of the effect of the same amount of the components when administered alone. This clear synergistic effect made it possible for this combination of two safe and non-toxic substances to give exactly the same antiinflammatory effect as betamethasone 17-valerate, one of the strongest topical steroids used to treat skin diseases, which may only be used for a few weeks at a time due to significant damaging effects on the skin, including atrophy and unhealable wounds. Today no safe alternatives exist for such products and the complexes of the invention may revolutionise the treatment of chronic inflammatory diseases. In another animal study (example 112) simulating chronic inflammatory skin disease, which is particularly difficult to treat, another complex according to the invention was tested against betamethasone 17-valerate. In this pharmacological model mild steroids like hydrocortisone have no measurable effects. All three doses of the complex of the invention gave a statistically significant and dose dependent inhibition of inflammation and in the highest dose, which can realistically safely be used in humans, the complex gave a 60% higher inhibition of dermal inflammation than betamethasone 17-valerate ( $p=0.0089$ , Mann-Whitney U test). In this study both

substances were administered in the maximum dose that can realistically be administered to humans, with the main difference that in the case of the complex of the invention, no toxic or adverse reactions can be anticipated, simply because the components of the complexes are biological molecules compatible with the human organism. Accordingly, the combination of a fatty acid ester of a polyhydroxyalkane and a pyridine carboxy derivative are of use generally in the immunomodulation of a mammal, such as a human. Furthermore, such combinations of components possess broad-spectrum antibacterial and fungicidal properties, thereby making them highly relevant for the treatment of a great number of infectious diseases and inflammatory skin diseases, including those diseases associated with secondary infections, which is a common problem with chronic inflammatory disease. The present inventor provides data herein demonstrating synergistic effects also in relation to antimicrobial effects. As demonstrated in example 113 a minimum inhibitory concentration (MIC) could be established against 5 organisms for the complex, while the individual components at the levels present in the complex could not demonstrate any measurable effect. Interestingly, the specific complex in question was able to significantly suppress a multi-resistant bacterium (methicillin resistant *Staphylococcus aureus*).

Contrarily to existing therapeutic agents, such as corticosteroids or non-steroidal anti-inflammatory drugs, the chemical complexes and pharmaceutical compositions according to the present invention have the advantage of not being likely to be associated with any serious side effects, as all of their components are non-toxic and well tolerated by the organism in the pharmacologically relevant doses.

Accordingly, the present invention provides a chemical complex or a pharmaceutical composition comprising:

i) a fatty acid ester of formula I or isomers thereof,



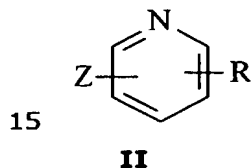
wherein n is 1, 2, 3, 4, 5 or 6;

each  $R^1$  and  $R^2$  is independently selected from the group consisting of H, OH, OM,  
5 OR', O-CO-R', optionally substituted straight-chain or branched  $C_1$ - $C_6$  alkyl and optionally substituted straight-chain or branched  $C_2$ - $C_6$  alkenyl,

wherein R' is selected from the group consisting of optionally substituted  $C_6$ - $C_{20}$  alkyl and optionally substituted  $C_6$ - $C_{20}$  alkenyl, and wherein M is an alkali metal;

10 provided that at least one of  $R^1$  and  $R^2$  is a group -O-CO-R' or -OR'; and

ii) a pyridine derivative of formula II or a salt thereof,



wherein R is one substituent selected from the group consisting of  $-C(=X)R_a''$  and  $-CH(R_b'')XH$ ;

20

wherein X is O or S,

$R_a''$  is selected from the group consisting of H, OH,  $OR'''$ ,  $NH_2$ ,  $NHR'''$ ,  $NR'''R''''$ ,  $CH_2COOH$ ,  $O^-Y^+$  and halogen,

25

$R_b''$  is selected from the group consisting of H and  $CH_2COOH$ ,

wherein  $R'''$  and  $R''''$  are independently selected from H, OH, , optionally substituted  $C_1$ - $C_{20}$  straight-chain, branched or cyclic alkyl, optionally containing  
30 one or more multiple bonds, and aryl, and wherein  $Y^+$  is a cation selected from optionally substituted mono-, di-, tri- or tetraalkylammonium ions, ammonium ion, and alkali metal ions,;

Z is present 0, 1, 2, 3, or 4 times and selected from the group consisting of hydrogen,  
35 halogen,  $NH_2$ , methyl,  $OR'''$  or -SH.

The chemical complexes and pharmaceutical compositions according to the invention may be employed for therapeutic applications such as i) immunomodulation, ii) the treatment of hypersensitivity diseases; iii) the treatment of inflammatory diseases, iv) the treatment of IgE mediated allergic reactions and conditions; v) the treatment of autoimmune disorders; 5 vi) the alleviation of pain; vii) the treatment of infectious diseases, e.g. bacterial, viral, or fungal infections and viii) the treatment inflammation associated with cancer.

An important aspect of the invention relates to the use of a combination of a fatty acid ester of a polyhydroxyalkane and a pyridine carboxy derivative for the preparation of a 10 product for the treatment of infections or diseases associated with infections selected from the group consisting of microbial infections, viral infections, infections caused by parasites, infections caused by fungi in a mammal, such as a human, as well as to a method for the treatment of infections or diseases associated with infections selected from the group consisting of microbial infections, viral infections, infections caused by parasites, infections 15 caused by fungi in a mammal, such as a human, comprising the administration of an effective amount of a combination of a fatty acid ester of a polyhydroxyalkane and a pyridine carboxy derivative, or a complex comprising said combination to said mammal.

Of particular interest is the treatment of viral and microbial infections or diseases 20 associated with infections caused by virus or a bacterie.

Still further aspects relate to anti-hypersensitivity and anti-inflammatory activity of said combination of a fatty acid ester and a pyridine carboxy derivative, for which reason said invention also relate to a method for the suppression of hypersensitivity and/or 25 inflammatory reaction in a mammal, such as the treatment of a disease and disorder associated with hypersensitivity and/or inflammatory reactions. Included herein is the treatment of hypersensitivity and/or inflammatory skin diseases in general and in particularly with respect to the treatment of pruritus, urticaria, of atopic eczema, contact dermatitis, seborrhoeic dermatitis, acne, rosacea, alopecia, vitiligo and/or psoriasis.

30 In still further aspects, the treatment of a hypersensitivity and/or an inflammatory conditions relates to the treatment of IgE mediated allergic reaction in general and particularly with respect to asthma, allergic rhinitis, and/or anaphylaxis; a method for the treatment of autoimmune disease and/or chronic inflammatory disease in general and 35 particularly with respect to diabetes, Crohn's disease, ulcerative colitis, rheumatoid arthritis, gout or osteoarthritis; a method for the treatment of cancer; and to a method for the alleviation of pain; each method comprising the administration of an effective amount of a combination of a fatty acid ester of a polyhydroxyalkane and a pyridine carboxy



derivative, or a complex or composition comprising said combination to a mammal, such as a human.

In still further aspects, the combination of a fatty acid ester and a pyridine carboxy derivative as disclosed herein is for use as a dietary supplement or a cosmetic, such as for example for the cosmetic treatment of conditions selected from the group consisting of acne, acne prone skin, irritated skin, dry skin, skin redness, scaly or flaking skin, sunburn or as an antiseptic agent, disinfectant, bacteriostatic agent, bactericidal agent, protective agent, and/or regenerating agent.

### DETAILED DESCRIPTION OF THE INVENTION

The present inventor provides data herein indicating that a combination of a fatty acid ester of polyhydroxyalkanes synergistically reduces the inflammation in a well-established *in vivo* test models of both acute and chronic inflammation. The reduction of inflammation was comparable to or even superior to one of the strongest topical steroids in clinical use at therapeutically relevant doses of betamethasone 17-valerate. Consequently, the combination of fatty acid esters of polyhydroxyalkanes and pyridine carboxy derivate is unexpectedly effective in suppressing hypersensitivity and inflammatory reactions. Moreover, surprisingly, the present combinations according to the invention were proved to be effective in inhibiting the growth of a number of microorganisms, including *Candida Albicans*, *Epidermophyton floccosum*, *Microsporum canis*, *Streptococcus faecalis* and *Trichophyton rubrum*. However, each of the individual tested components of the complex did not inhibit growth, for which reason the present combination of fatty acid esters of polyhydroxyalkanes and pyridine carboxy derivate seems to have a synergistic effect also with respect to suppression of microbial growth. Also very surprisingly, the present inventor found that combinations according to the invention inhibited the growth of resistant *Staphylococcus Aureus*.

Hence, the combination of a fatty acid ester of a polyhydroxyalkane and a pyridine carboxy derivative significantly suppresses hypersensitivity reactions and/or inflammatory reactions. Such chemical complexes are novel and provide a surprisingly good anti-hypersensitivity and anti-inflammatory effect with a surprisingly good safety profile. Simultaneously, the complexes of the invention provide strong antimicrobial effects, especially in topical application, with a surprisingly broad spectrum of activity against pathogenic bacteria and fungi and with a surprisingly low toxicity for humans providing an excellent safety profile. Thus the chemical complexes or compositions of the invention are virtually non-toxic and yet very therapeutically effective.

According to the invention, said combination of a fatty acid ester of a polyhydroxyalkane and a pyridine carboxy derivative may be provided in the form of a chemical complex. Without being limited to a particular theory, the combination is advantageous provided as a chemical complex for purposes of achieving homogeneous mixtures of the two agents, 5 thereby positively affecting the resulting therapeutic effect. Furthermore, said combination of a fatty acid ester of a polyhydroxyalkane and a pyridine carboxy derivative may be provided as a pharmaceutical composition, dietary supplement or a cosmetic, wherein said combination may be in a chemical complex form or just mixtures of the two individual agents. In some embodiments thereof, said combination of a fatty acid ester of a 10 polyhydroxyalkane and a pyridine carboxy derivative may each be provided in separate compositions.

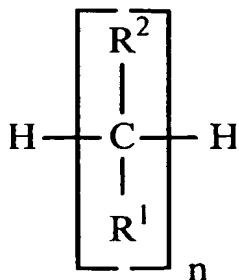
Such combinations of fatty acid ester of a polyhydroxyalkane and a pyridine carboxy derivative as well as compositions and chemical complexes of said combination are novel 15 and provide a surprisingly effective anti-hypersensitivity and anti-inflammatory effect with a surprisingly good safety profile. Thus the chemical complexes or compositions of the invention are virtually non-toxic and yet very therapeutically effective.

The present inventor proposes the hypothesis that the very advantageous therapeutic 20 index of the combination of a fatty acid ester of a polyhydroxyalkane and a pyridine carboxy derivative in comparison to the individual anti-hypersensitivity or antimicrobial drugs is due to any synergistic effect or complementary effects between the components of the combinations. Thus, this results in a lower toxic load on the body in comparison to any single chemical compound, while still achieving a surprisingly good therapeutic effect. 25

The invention is based, at least in part, on the synergistic between the pyridine carboxy derivative and the fatty acid ester of a polyhydroxyalkane in comparison to either component. This surprising synergism allows for the combining of any fatty acid ester of a polyhydroxyalkane with an optionally substituted pyridine carboxy derivative to achieve 30 the desired effect at much lower doses than ever anticipated. Moreover, the synergism allows for the use of a fatty acid ester of a polyhydroxyalkane or a pyridine carboxy derivative previously not used for the desired effect due to the high doses required to achieve said effect. Still further, this synergism allows for the use of compounds, which are not used due to the toxicity associated with therapeutically effective doses.

35 The present invention provides a chemical complex or a pharmaceutical composition comprising:

i) a fatty acid ester of formula I or isomers thereof,

**I**

5 wherein n is 1, 2, 3, 4, 5 or 6;

each R<sup>1</sup> and R<sup>2</sup> is independently selected from the group consisting of H, OH, OM, OR', O-CO-R', optionally substituted straight-chain or branched C<sub>1</sub>-C<sub>6</sub> alkyl and optionally substituted straight-chain or branched C<sub>2</sub>-C<sub>6</sub> alkenyl,

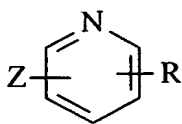
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wherein R' is selected from the group consisting of optionally substituted C<sub>6</sub>-C<sub>20</sub> alkyl and optionally substituted C<sub>6</sub>-C<sub>20</sub> alkenyl, and wherein M is an alkali metal;

provided that at least one of R<sup>1</sup> and R<sup>2</sup> is a group -O-CO-R' or -OR'; and

15

ii) a pyridine derivative of formula II or a salt thereof,



20

**II**

wherein R is one substituent selected from the group consisting of -C(=X)R<sub>a</sub><sup>''</sup> and -CH(R<sub>b</sub><sup>''</sup>)XH;

25

wherein X is O or S,

R<sub>a</sub><sup>''</sup> is selected from the group consisting of H, OH, OR<sup>'''</sup>, NH<sub>2</sub>, NHR<sup>'''</sup>, NR<sup>'''</sup>R<sup>''''</sup>, CH<sub>2</sub>COOH, O<sup>-</sup>Y<sup>+</sup> and halogen,

30

R<sub>b</sub><sup>''</sup> is selected from the group consisting of H and CH<sub>2</sub>COOH,

wherein R''' and R'''' are independently selected from H, OH, , optionally substituted C<sub>1</sub>-C<sub>20</sub> straight-chain, branched or cyclic alkyl, optionally containing one or more multiple bonds, and aryl, and wherein Y<sup>+</sup> is a cation selected from  
5 optionally substituted mono-, di-, tri- or tetraalkylammonium ions, ammonium ion, and alkali metal ions,;

Z is present 0, 1, 2, 3, or 4 times and selected from the group consisting of hydrogen, halogen, NH<sub>2</sub>, methyl, OR''' or -SH.

10

The term "chemical complex" is intended to include the definition defined by IUPAC that read as follows:

*"A molecular entity formed by loose association involving two or more component molecular entities (ionic or uncharged), or the corresponding chemical species. The  
15 bonding between the components is normally weaker than in a covalent bond." (IUPAC Compendium of Chemical Terminology 2nd Edition (1997))*

Thus, the term "chemical complex" is intended to mean any combination of the component molecules in the context of the IUPAC definition. It is not intended to imply an ionic  
20 association or covalent association between the components. Also as used herein, the chemical complex of the present invention relates to a complex obtainable from the combining of a pyridine carboxy derivative of Formula II and a fatty acid ester of a polyhydroxy alkane of Formula I.

25 The practical and technical implementation of the IUPAC chemical complex definition is that the product is homogeneous at the molecular level and does not for example consist of microphases. An appropriate method for studying a chemical complex will vary from complex to complex but typical methods are x-ray diffraction, differential scanning calorimetry and electron microscopy.

30

As mentioned, the pyridine carboxy derivative may optionally be substituted. The term "optionally substituted" is intended to mean the substitution of one or more hydrogen atoms is substituted with another atom, chemical group or entity, termed substituents. Illustrative examples of substituents include carboxyl, formyl, amino, hydroxyl, halogen,  
35 nitro, sulphonyl, sulphonyl, C1-6-alkyl, aryl, aryloxy, aryloxycarbonyl, arylcarbonyl, heteroaryl, amino, mono- and di(C1-6-alkyl)amino; carbamoyl, mono- and di(C1-6-alkyl)aminocarbonyl, amino-C1-6-alkyl-aminocarbonyl, mono- and di(C1-6-alkyl)amino-C1-6-alkyl-aminocarbonyl, C1-6-alkylcarbonylamino, cyano, guanidino, carbamido, C1-6-

alkanoyloxy, C1-6-alkylsulphonyloxy, dihalogen-C1-6-alkyl, trihalogen-C1-6-alkyl, C1-6-alkoxyl, oxo, C1-6-carboxyl, C1-6-alkoxycarbonyl, C1-6-alkylcarbonyl, where aryl and heteroaryl representing substituents may be substituted 1-5 times with C1-6-alkyl, C1-6-alkoxy, nitro, cyano, hydroxy, amino or halogen. In general, the above  
5 substituents may be susceptible to further optional substitution.

The term "C<sub>1</sub>-C<sub>20</sub> alkyl" is intended to mean a linear or branched saturated hydrocarbon chain wherein the longest chains has from one to twenty carbon atoms, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl,  
10 neopentyl, hexyl, heptyl, octyl, undecacyl, dodecyl, etc. A branched hydrocarbon chain is intended to mean a C<sub>1</sub>-C<sub>20</sub> alkyl substituted at any carbon with a hydrocarbon chain. The C<sub>1</sub>-C<sub>20</sub> alkyl chain of the present invention may be optionally substituted.

The term "C<sub>2</sub>-C<sub>20</sub> alkenyl" is intended to mean a linear or branched unsaturated  
15 hydrocarbon chain with one or more double bindings and wherein the longest chains has from one to twenty carbon atoms. A branched hydrocarbon chain is intended to mean a C<sub>1</sub>-C<sub>20</sub> alkyl substituted at any carbon with a hydrocarbon chain. The C<sub>2</sub>-C<sub>20</sub> alkenyl chain of the present invention may be optionally substituted.

20 The term "C<sub>1</sub>-C<sub>20</sub> alkoxy" is intended to mean a linear or branched hydrocarbon chain wherein the longest chains has from one to twenty carbon atoms, such as methoxy, ethoxyl, n-propoxyl, isopropoxyl, n-butoxyl, isobutoxyl, isopentoxyl, hexoxyl, heptoxyl, octoxyl, etc. A branched hydrocarbon chain is intended to mean a C<sub>1</sub>-C<sub>20</sub> alkyl substituted at any carbon with a hydrocarbon chain. The C<sub>1</sub>-C<sub>20</sub> alkyl chain of the present invention  
25 may be optionally substituted.

The term "halogen" includes fluorine, chlorine, bromine and iodine.

Concerning the fatty acid derivative of the invention, it is to be understood that suitable  
30 embodiments include those wherein at least one of R<sub>1</sub>, R<sub>2</sub> and R<sub>3</sub> is OH. Furthermore, still interesting embodiments include those wherein at most two of R<sub>1</sub>, R<sub>2</sub> and R<sub>3</sub> is O-CO-R', preferably one such group. Thus, mono and di-esters of fatty acids and a polyhydroxyalkane are anticipated. In some embodiments thereof, two different fatty acids may be esterified to the polyhydroxyalkane and in other embodiments the fatty acids are  
35 identical.

Furthermore, it is to be understood that the ester group, O-CO-R', may be replaced by a ether group, -OR'. Thus, in a further aspect of the invention, the compositions or chemical complexes of the invention comprises an alkylether of a polyhydroxyalkane.

As stated, the esters according to formula I comprise at least one ester group, O-CO-R', wherein R' is an alkyl or an alkenyl with a carbon chain length of at most 20 carbon atoms. However, in suitable embodiments of the invention, the R' are shorter than twenty carbon atoms or longer than one or two carbon atoms. Thus, in various separate embodiments R' is selected from C<sub>3</sub>-C<sub>18</sub> alkyl and C<sub>3</sub>-C<sub>18</sub> alkenyl; C<sub>4</sub>-C<sub>16</sub> alkyl and C<sub>4</sub>-C<sub>16</sub> alkenyl; C<sub>4</sub>-C<sub>16</sub> alkyl and C<sub>4</sub>-C<sub>16</sub> alkenyl; C<sub>6</sub>-C<sub>12</sub> alkyl and C<sub>6</sub>-C<sub>12</sub> alkenyl; C<sub>6</sub>-C<sub>10</sub> alkyl and C<sub>6</sub>-C<sub>10</sub> alkenyl; C<sub>2</sub>-C<sub>10</sub> alkyl and C<sub>2</sub>-C<sub>10</sub> alkenyl; and C<sub>4</sub>-C<sub>10</sub> alkyl and C<sub>4</sub>-C<sub>10</sub> alkenyl.

10

As mentioned, each R<sup>1</sup> and R<sup>2</sup> may independently be selected from the group consisting of H, OH, OM, OR', O-CO-R', optionally substituted straight-chain or branched C<sub>1</sub>-C<sub>6</sub> alkyl and optionally substituted straight-chain or branched C<sub>2</sub>-C<sub>6</sub> alkenyl, wherein M is an alkali metal, such as sodium, potassium or ammonium.

15

In some suitable embodiments, the group, O-CO-R' is an acyloxy moiety derived from an acid, HO-CO-R', that may be selected from the group consisting of caproic acid, caprylic acid, capric acid, lauric acid, myristic acid, myristoleic acid, palmitic acid, palmitoleic acid, linoleic acid,  $\alpha$ -linolenic acid,  $\gamma$ -linolenic acid and ricinoleic acid.

20

Furthermore, the O-CO-R' may be an acyloxy moiety derived from an acid, HO-CO-R', selected from the group consisting of all-*cis*-5,8,11,14,17-eicosapentaenoic acid and docosahexaenoic acids (DHA).

25 As stated, the fatty acid ester is connected with an polyhydroxyalkane of various carbon length such that wherein n is 1, 2, 3, 4, 5 or 6. Preferably, n may be 1, 2 or 3. Typical examples of polyhydroxyalkanes of interest include propylene glycol, glycerol, 1,3-butylene glycol, 2,3-butylene glycol or sorbitol.

30 The fatty acid ester of a polyhydroxyalkane, for illustrative purposes, may be selected from the group consisting of Ethyleneglycyl-1-hexanoate, Ethyleneglycyl-1-(4-noneoate), Glyceryl-2-(5-ethyl-octanoate), Trimetyleneglycyl-1-dodecanoate-2-dodecanoate, Trimetyleneglycyl-1-octadecanoate-2-(5,7,9-heptadecatrienoate), 1,2,3,4-butanetraol-1-undecanoate-3-nonanoate, 1-ol-2,3-butylenglycyl-1-heptandecanoate-2-heptandecanoate, 35 Propylenglycyl- 2-(3-metyl-decanoate), 1,2-butylenglycyl-1-hexanoate-2-hexanoate, Ethyleneglycyl-1-octanoate, Ethylenglycyl-1-octanoate-4-(3-ethyl-hexanoate, 1,2,3,4-butanetraol-1-hexadecanoate-(4-(2,4-diethyl-8-hexadecenoate), 1,2,3,4-butanetraol-2-eicosatrienoate, Glyceryl-1-decanoate-2-decanoate, 1,4-butylenglycyl-1-octanoate, 1-ol-2,3-butylenglycyl-1-heptandecanoate-2-heptandecanoate, Propylenglycyl-1-undecanoate-

2-undecanoate, Propylenglycyl-1-(7,10-octadecadienoate)-2-octanoate, Glyceryl-2-(8,11,14-eicosatrienoate), Ethylenglycyl-1-decanoate-2-hexanoate, Ethylenglycyl-1-(4-tetradecenoate), Glyceryl-1-octanoate-3-undecanoate, Glyceryl-1-(4-nonenoate)-3-hexanoate, Trimethylglycyl-1-octanoate, Trimethylenglycyl-1-undecanoate, Propylenglycyl-1-  
5 hexanoate, Propylenglycyl-2-(3-methyl-decanoate), 1,2-butylenglycyl-2-octanoate, 1,2-butylenglycyl-1-nonanoate-2-octanoate, 1,3-butylenglycyl-1-decanoate-3-octanoate, 2,3-butylenglycyl-2-dodecanoate, 2,3-butylenglycyl-2-octanoate-3-octanoate, Ethylenglycyl-1-(3,6-octadecadienoate)-2-octanoate, Ethylenglycyl-1-(8-methyl-3,6-octadecadienoate), Glyceryl-1-(4,6,10-eicosatrienoate)-2-(4,6,10-eicosatrienoate), Glyceryl-1-(8-  
10 octadecenoate)-3-heptanoate, Trimethylenglycyl-2-(4-methyl-2,8-eicosadienoate), Propylenglycyl-1-nonanoate, 1,2,3,4-butanetraol-1-decanoate, 1,2,3,4-butanetraol-1-hexadecanoate-(4-(2,4-diethyl-8-hexadecenoate), 1,2,3,4-butanetraol-2-eicosatrienoate, 2,3-butylenglycyl-2-hexanoate, 1-ol-2,3-butylenglycyl-1-(4-methyl-hexanoate), 1-ol-2,3-butylenglycyl-1-(3-octenoate), 1,4-butylenglycyl-1-dodecanoate,  
15 1,4-butylenglycyl-1-decanoate-4-decanoate, 1,2,3,4-butanetraol-2-(2-methyl-octanoate), 1,2,3,4-butanetraol-1-hexanoate-2-hexanoate, Glyceryl-2-(3,5,7-hexadecatrienoate), Glyceryl-1-octanoate, Glyceryl-2-octanoate, Glyceryl-2-octanoate, Glyceryl-1-octanoate-2-octanoate, Glyceryl-2-(3,5,7-hexadecatrienoate), Glyceryl-1-(3-ethyl-2-methyl-8,10-eicosadienoate)-2-octanoate, Propylenglycyl-1-(2,4-ethyl-6-tetradecaenoate)-2-(8,12-  
20 hexadecaenoate), 1,2-butylenglycyl-1-decanoate, 1,2-butylenglycyl-1-heptadecanoate-2-(4,8-heptadecadienoate), 1,2-butylenglycyl-1-(8-ethyl-4-methyl-6,16-octadecadienoate), Glyceryl-1-(5,8,11,14,17-eicosapentaenoate), Propylenglycyl-1-nonanoate-2-decanoate, Trimethylenglycyl-1-octanoate-2-(4-ethyl-decanoate), 1,3-butylenglycyl-1-undecanoate, 1,3-butylenglycyl-3-hexanoate, 1,3-butylenglycyl-1-octanoate-3-octanoate, 1-ol-2,3-  
25 butylenglycyl-1-undecanoate-2-undecanoate, 1-ol-2,3-butylenglycyl-1-(2-ethyl-nonanoate)-2-hexanoate, Glyceryl-2-octanoate, Glyceryl-1-octanoate-2-octanoate, 1,4-butylenglycyl-1-octanoate-4-heptanoate, 2,3-butylenglycyl-2-dodecanoate-3-heptanoate, 1,2,3,4-butanetraol-2-(2-methyl-octanoate), 1,2,3,4-butanetraol-1-hexanoate-2-hexanoate, 1,4-butylenglycyl-1-(6,10,12,18-tetradecantetraenoate)-4-(4,8-dimethyl-6,13-  
30 eicosadienoate), 1,4-butylenglycyl-1-(2-ethyl-octanoate)-4-(4-nonenoate), Glyceryl-1-octanoate, Glyceryl-1-(5,8,11,14,17-eicosapentaenoate), Glyceryl-2-(8,11,14-eicosatrienoate), 1,2,3,4-butanetraol-2-(2-methyl-octanoate), Ethyleneglycyl-1-octanoate, Ethylenglycyl-1-octanoate-4-(3-ethyl-hexanoate), Glyceryl-1-octanoate, Glyceryl-1-(5,8,11,14,17-eicosapentaenoate), Glyceryl-2-(8,11,14-eicosatrienoate), Glyceryl-2-  
35 (8,11,14-eicosatrienoate), 1,2,3,4-butanetraol-2-(2-methyl-octanoate), Glyceryl-1-octanoate, Trimethylenglycyl-2-(4-methyl-2,8-eicosadienoate), Propylenglycyl-1-nonanoate, Glyceryl-1-(5,8,11,14,17-eicosapentaenoate), Propylenglycyl-1-(2,4-ethyl-6-tetradecaenoate)-2-(8,12-hexadecaenoate), 1,2-butylenglycyl-1-decanoate, 1,2-butylenglycyl-2-octanoate, Glyceryl-2-octanoate, 1,4-butylenglycyl-1-decanoate-4-

decanoate, Glyceryl-2-octanoate, Ethylenglycyl-1-decanoate-2-hexanoate, 1-ol-2,3-butylenglycyl-1-(2-ethyl-nonanoate)-2-hexanoate, Glyceryl-2-(8,11,14-eicosatrienoate), derivatives and salts thereof.

- 5 In currently preferred embodiments of the invention, the fatty acid ester of the invention is racemic, enantiomerically enriched or enantionerically pure 1-glyceryl-monocaprylate and niacinamide, preferably when provided in a molar ratio 2:7 or 1:14.

As used herein, the pyridine carboxy derivative includes salts of compounds of formula II.

- 10 The salts may be any pharmaceutically acceptable salt including hydrates, solvent addition forms, acid addition salts. In different embodiments of the invention, the salt is a hydroiodide, hydrochloride or a hydrobromide, e.g. nicotinamide hydroiodide.

The term "base addition salts" include alkali metals, such as sodium and potassium, alkali

- 15 earth metals, such as calcium and magnesium, and organic addition salts such as quaternary ammonium cations.

As stated, the complex comprises, in part, the optionally substituted pyridine carboxy derivative according to Formula II wherein R is one substituent selected from the group

- 20 consisting of  $-C(=X)R_a''$  and  $-CH(R_b'')XH$ , wherein X is O or S and  $R_a''$  is selected from the group consisting of H, OH,  $OR'''$ ,  $NH_2$ ,  $NHR'''$ ,  $NR'''R''''$ ,  $CH_2COOH$ ,  $O^-Y^+$  and halogen.  $R_b''$  is selected from the group consisting of H and  $CH_2COOH$ .  $R'''$  and  $R''''$  may independently be selected from H, OH, optionally substituted  $C_1$ - $C_{20}$  straight-chain, branched or cyclic alkyl, optionally containing one or more multiple bonds, and aryl. Thus,  $R'''$  and  $R''''$  may
- 25 independently be selected from optionally substituted  $C_1$ - $C_{20}$  alkyl, optionally substituted  $C_1$ - $C_{20}$  alkoxy and optionally substituted  $C_2$ - $C_{20}$  alkenyl. In suitable embodiments, the carbon chain length of  $R'''$  and  $R''''$  are shorter than twenty carbon atoms, e.g. from  $C_1$ - $C_{10}$ ,  $C_1$ - $C_8$ ,  $C_1$ - $C_6$ ,  $C_1$ - $C_4$  or  $C_1$ - $C_3$ . With respect to the optionally substituted alkenyls, the carbon chain length is at least two carbon and may comprise one or more double bonds such as 1,
- 30 2, or 3 double bonds. Thus, the optionally substituted alkenyls can have any length, e.g. from  $C_2$ - $C_{12}$ ,  $C_2$ - $C_{10}$ ,  $C_2$ - $C_8$ ,  $C_2$ - $C_6$ ,  $C_2$ - $C_4$  or  $C_2$ - $C_3$ . In suitable embodiments  $R'''$  and  $R''''$  may independently be selected from the group consisting of optionally substituted  $C_1$ - $C_{10}$  alkyl and optionally substituted  $C_2$ - $C_{10}$  alkenyl and  $R_a''$  may be  $OR'''$ ,  $NH_2$ ,  $NHR'''$  or  $NR'''R''''$  wherein  $R'''$  and  $R''''$  may be independently selected from the group consisting of optionally
- 35 substituted  $C_1$ - $C_6$  alkyl and optionally substituted  $C_2$ - $C_6$  alkenyl. Also  $R'''$  may be selected from optionally substituted  $C_1$ - $C_4$  alkyl and optionally substituted  $C_1$ - $C_4$  alkenyl.



Furthermore, the pyridine carboxy derivative may be subjected to repeatedly ring substitution, such that Z is present 0, 1, 2, 3, or 4 times and selected from the group consisting of hydrogen, halogen,  $\text{NH}_2$ , methyl,  $\text{OR}'''$  or  $-\text{SH}$ . Preferably, Z is 0 or 1.

- 5 In still further interesting embodiments, the pyridine derivative is a pyridine-3-carboxy derivative, i. e. R is located at the 3-position.

The optionally substituted pyridine carboxy derivative may, for illustrative purposes, be selected from the group consisting of optionally substituted nicotinic acid, its corresponding  
10 acyl halide, ester, acid salt, or amide, nicotinamide; optionally substituted isonicotinic acid, its corresponding acyl halide, ester, acid salt, or amide, isonicotinamide; and optionally substituted picolinic acid, its corresponding acyl halide, ester, acid salt, or amide, picolinamide.

- 15 In very interesting embodiments of the invention, the pyridine carboxy derivative is pyridine-3-carboxy derivative. Hence, in different embodiments of the invention, the pyridine carboxy derivative is selected from the group consisting of niacinamide, thioniacinamide, 6-aminoniacinamide,  $\text{N}^2$ -methylniacinamide,  $\text{N}^2$ -ethylniacinamide, nicotinic acid, 6-methoxy-niacinamide and salts thereof. Moreover, it is also anticipated  
20 that polymeric forms of nicotinic acid may be applicable. Thus, in one embodiment the pyridine derivative is inosital hexaniacinate which can be viewed as a prodrug. Moreover, quinolinic acid imide, nicotinanilide, nifhenazone, nialamide, 1-(3-pyridylmethyl) urea, nicomol and niaprazine or derivatives thereof is of interest for use as a pyridine carboxy derivative.

25

As stated above, these pyridine carboxy derivatives may optionally be further substituted or they may be provided as salts. In some embodiments, the pyridine ring may be substituted with an amino group or alkoxy group.

- 30 In the embodiment where the optionally substituted pyridine carboxy derivative is an amide, the amide may be its free primary amide ( $\text{NH}_2$ ), its secondary amide ( $\text{NHR}'''$ ) or its tertiary amide ( $\text{NR}''' \text{R}'''$ ).

- As stated, the pyridine carboxy derivative may be optionally substituted. In one suitable  
35 embodiment, the pyridine carboxy is further substituted with a carboxy group such as a carboxylic acid. Moreover, in interesting embodiments the pyridine carboxy is further substituted with alkoxyl, e.g. methoxy and ethoxy, amino, acyl, halide, carboxylic ester, or acetamide. The pyridine carboxy may be substituted 0 to 4 times, such as 0, 1, 2, 3, or 4

times, preferably 0 to 1 time, most preferably 0 times. In one embodiment thereof the pyridine carboxy derivative is 6-amino-nicotinamide or 6-methoxy-nicotinamide.

In a suitable embodiment of the invention, the chemical complex and the composition  
5 comprises more than one pyridine carboxy derivative.

As stated, the complex comprises, in part, the fatty acid ester of a polyhydroxyalkane. In a suitable embodiment of the invention, the chemical complex and the composition  
comprises more than one fatty acid ester of a polyhydroxyalkane.

10

As stated the combination of the two agents provides a surprisingly effective therapeutic agent for suppression of hypersensitivity and inflammatory reactions. The proper therapeutic efficacy may, in part, be adjusted by providing the two agents in suitable molar ratios or mass ratios.

15

Hence, the combination of a fatty acid ester of a polyhydroxyalkane and the pyridine carboxy derivative in a chemical complex or in a compositions according to the invention comprises adjustable molar ratio's between fatty acid ester of a polyhydroxyalkane and the pyridine carboxy derivative in the range of about 1:10000 to 10000:1. Preferably in  
20 the range of about 1:1000 to 1000:1, such as about 1:500 to 500:1, such as 1:100 to 100:1, about 1:50 to 50:1, or about 1:40 to 40:1, also about 1:30 to 30:1, such as about 1:25 to 25:1, about 1:20 to 20:1, about 1:18 to 18:1, about 1:16 to 16:1, about 1:14 to 14:1, or about 1:12 to 1:12, also about 1:10 to 10:1, such as about 1:9 to 9:1, about 1:8 to 8:1, about 1:7 to 7:1, about 1:6 to 6:1, also from 1:5 to 5:1, such as from 1:4 to 4:1,  
25 e.g. from 1:3 to 3:1, such as from 1:2 to 2:1.

Alternatively defined, the ratio between the fatty acid ester of a polyhydroxyalkane and the pyridine carboxy derivative may be expressed as a mass ratio. The mass ratio between the fatty acid ester of a polyhydroxyalkane and the pyridine carboxy derivative may be about  
30 1:10000 to 10000:1, preferably about 1:1000 to 1000:1, such as about 1:500 to 500:1, such as 1:100 to 100:1, about 1:50 to 50:1, or about 1:40 to 40:1, also about 1:30 to 30:1, such as about 1:25 to 25:1, about 1:20 to 20:1, about 1:18 to 18:1, about 1:16 to 16:1, about 1:14 to 14:1, or about 1:12 to 1:12, also about 1:10 to 10:1, such as about 1:9 to 9:1, about 1:8 to 8:1, about 1:7 to 7:1, about 1:6 to 6:1, also from 1:5 to 5:1,  
35 such as from 1:4 to 4:1, e.g. from 1:3 to 3:1, such as from 1:2 to 2:1.

For the administration to a mammal, such as a human, the chemical complex may be administered directly, eventually provided in a capsule or the like. More convenient, the complex may be formulated into a composition comprising the chemical complex and

optionally, one or more acceptable excipients. Alternatively, the combination of the two agents may also be formulated into a composition without being provided as a chemical complex. Thus, in some embodiments of the invention, the chemical complexes or compositions further comprise one or more excipient(s) or carrier(s), preferably  
5 pharmaceutically acceptable excipient(s) or carrier(s).

- According to the invention, the above-mentioned chemical complexes or compositions may be combined with any other therapeutically active agents in order to strengthen, improve, potentiate, or prolong the therapeutic actions of said complexes and said compositions.
- 10 Thus according to the invention, the composition may further comprise one or more therapeutically active agents. Therapeutically active agents of interest include those selected from the group consisting of antioxidants, steroids, antibiotics, anti-inflammatory agents and NSAID's.
- 15 The compositions according to the present invention may be further comprises one or more excipient(s) or carrier(s) for the formulation of the composition as a pharmaceutical, a dietary supplement or a cosmetic.

Thus, further aspects of the invention relates to the use of the combination of a fatty acid  
20 ester and a pyridine carboxy derivative as disclosed herein for use as a dietary supplement and/or a cosmetic. As is to be understood, the present combinations of components exhibit surprisingly activity in the alleviation of inflammation and infective conditions. Therefore, in further aspects, the invention relates to the cosmetic treatment of conditions that may be selected from the group consisting of acne, acne prone skin, irritated skin, dry skin,  
25 skin redness, scaly or flaking skin, and sunburned skin. Moreover, as may be understoodm the present combination of components as disclosed herein may be used as an antiseptic agent, disinfectant, bacteriostatic agent, bactericidal agent, protective agent, and/or regenerating agent.

- 30 It is to be understood that the composition may be administered in several manners. Typically, a pharmaceutical may be formulated for oral, topical, transdermal, or parenteral administration, preferably oral or topical administration. The compositions according to the present invention may be formulated as a pharmaceutical composition for oral, topical, transdermal, or parenteral administration, preferably oral or topical administration.

35

In a suitable embodiment of the invention, the compositions are used for oral administration. In another suitable embodiment of the invention the compositions are used for topical administration.

Concerning compositions for cosmetic use, they may be formulated for application to skin or a mucous membrane such as to application to the mucous of the vagina, rectum, mouth or eyes. Moreover, the cosmetic use may imply peroral formulations of the compositions. Typically, the cosmetic formulations may be in the form of creams, lotions, gels, shampoo, conditioner, fluid soap, bar soap, cleansing products, shower and bath products.

In a preferred embodiment of the invention the compositions are formulated for topical administration (e.g. to the skin) in the form of emulsions (e.g. creams or lotions), gels, solutions, liniments, ointments, sprays, aerosols or powders.

10

The fatty acid ester of a polyhydroxyalkane and the pyridine carboxy derivative may together be comprised in a single formulation or may each individually be comprised in separate formulations. The separate formulations may be administered in a simultaneous or non-simultaneous manner. As stated, the fatty acid ester of a polyhydroxyalkane and the pyridine carboxy derivative are together comprised in a single formulation.

15

The active ingredients of the chemical complex or pharmaceutical composition of the present invention need not be administered as one pharmaceutical entity, but may of course be administered as individual compounds or pharmaceutical compositions.

In addition to the formulations described previously, the compositions of the invention may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compositions may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

20

The pharmaceutical compositions for oral, topical, transdermal, or parenteral administration may be in form of, e.g., solid, semi-solid or fluid compositions and formulated according to conventional pharmaceutical practice, see, e.g., "Remington: The science and practice of pharmacy" 20<sup>th</sup> ed. Mack Publishing, Easton PA, 2000 ISBN 0-912734-04-3 and "Encyclopedia of Pharmaceutical Technology", edited by Swarbrick, J. & J. C. Boylan, Marcel Dekker, Inc., New York, 1988 ISBN 0-8247-2800-9.

30

The choice of pharmaceutically acceptable excipients in a composition for use according to the invention and the optimum concentration thereof is determined on the basis of the selection of the Fatty acid ester of a polyhydroxyalkane, selection of the pyridine carboxy derivative, the kind of dosage form chosen and the mode of administration. However, a

35

person skilled in the art of pharmaceutical formulation may find guidance in e.g., "Remington: The science and practice of pharmacy" 20<sup>th</sup> ed. Mack Publishing, Easton PA, 2000 ISBN 0-912734-04-3. A pharmaceutically acceptable excipient is a substance, which is substantially harmless to the individual to which the composition will be administered.

- 5 Such an excipient suitably fulfils the requirements given by the national drug agencies. Official pharmacopeias such as the British Pharmacopeia, the United States of America Pharmacopeia and the European Pharmacopeia set standards for well-known pharmaceutically acceptable excipients.
- 10 For topical, trans-mucosal and trans-dermal compositions, such as administration to the mucosa or the skin, the compositions for use according to the invention may contain conventional non-toxic pharmaceutically acceptable carriers and excipients including microspheres and liposomes.
- 15 The topical, trans-mucosal and trans-dermal compositions for use according to the invention include an array of solid, semi-solid and fluid compositions. Compositions of particular relevance are e.g. pastes, ointments, hydrophilic ointments, creams, gels, hydrogels, solutions, emulsions, suspensions, lotions, liniments, resorbibles, suppositories, enema, pessaries, moulded pessaries, vaginal capsules, vaginal tablets, shampoos, jellies,
- 20 soaps, sticks, sprays, powders, films, foams, pads, sponges (e.g. collagen sponges), pads, dressings (such as, e.g., absorbent wound dressings), drenches, bandages, plasters and transdermal delivery systems.

The pharmaceutically acceptable excipients for topical, trans-mucosal and trans-dermal

25 compositions may include solvents, buffering agents, preservatives, humectants, chelating agents, antioxidants, stabilizers, emulsifying agents, suspending agents, gel-forming agents, ointment bases, suppository bases, penetration enhancers, perfumes, skin protective agents, diluents, disintegrating agents, binding agents, lubricants and wetting agents.

30

The oral compositions for use according to the invention include an array of solid, semi-solid and fluid compositions. Compositions of particular relevance are e.g. solutions, suspensions, emulsions, uncoated tablets, immediate-release tablets, modified-release tablets, gastro-resistant tablets, orodispersible tablets, effervescent tablets, chewable

35 tablets, soft capsules, hard capsules, modified-release capsules, gastro-resistant capsules, uncoated granules, effervescent granules, granules for the preparation of liquids for oral use, coated granules, gastro-resistant granules, modified-release granules, powders for oral administration and powders for the preparation of liquids for oral use.

The pharmaceutically acceptable excipients may include solvents, vegetable or marine oils (e.g. edible oils like almond oil, castor oil, cacao butter, coconut oil, corn oil, cottonseed oil, linseed oil, olive oil, palm oil, peanut oil, poppyseed oil, rapeseed oil, sesame oil, soybean oil, sunflower oil, and teaseed oil), mineral oils, fatty oils, liquid paraffin, buffering  
5 agents, preservatives, humectants, chelating agents, antioxidants, stabilizers, emulsifying agents, suspending agents, gel-forming agents, diluents, disintegrating agents, binding agents, lubricants, coating agents and wetting agents.

Typical solvents may be selected from the group comprising water, alcohols, polyethylene  
10 glycols, propylene glycols, glycerol, liquid polyalkylsiloxanes, and mixtures thereof.

Typical buffering agents may be selected from the group comprising of citric acid, acetic acid, tartaric acid, lactic acid, hydrogenphosphoric acid, diethylamine etc.

15 Typical preservatives may be selected from the group comprising parabens, such as methyl, ethyl, propyl p-hydroxybenzoate, butylparaben, isobutylparaben, isopropylparaben, potassium sorbate, sorbic acid, benzoic acid, methyl benzoate, phenoxyethanol, bronopol, bronidox, MDM hydantoin, iodopropynyl butylcarbamate, EDTA, benzalconium chloride, and benzylalcohol, or mixtures of preservatives.

20

Typical humectants may be selected from the group comprising glycerin, propylene glycol, sorbitol, lactic acid, urea, and mixtures thereof. Typical chelating agents are but not limited to sodium EDTA and citric acid. Typical antioxidants may be selected from the group comprising butylated hydroxy anisole (BHA), ascorbic acid and derivatives thereof,  
25 tocopherol and derivatives thereof, cysteine, and mixtures thereof. Suitable emulsifying agents may be selected from the group comprising naturally occurring gums, e.g. gum acacia or gum tragacanth; naturally occurring phosphatides, e.g. soybean lecithin; sorbitan monooleate derivatives; wool fats; wool alcohols; sorbitan esters; monoglycerides; fatty alcohols, fatty acid esters (e.g. triglycerides of fatty acids); and mixtures thereof.

30

Suitable suspending agents may be selected from the group comprising celluloses and cellulose derivatives such as, e.g., carboxymethyl cellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, carrageenan, acacia gum, arabic gum, tragacanth, and mixtures thereof.

35

Suitable gel bases and viscosity-increasing components may be selected from the group comprising liquid paraffin, polyethylene, fatty oils, colloidal silica or aluminium, zinc soaps, glycerol, propylene glycol, tragacanth, carboxyvinyl polymers, magnesium-aluminium silicates, Carbopol®, hydrophilic polymers such as, e.g. starch or cellulose derivatives such

as, e.g., carboxymethylcellulose, hydroxyethylcellulose and other cellulose derivatives, water-swellaable hydrocolloids, carragenans, hyaluronates (e.g. hyaluronate gel optionally containing sodium chloride), and alginates including propylene glycol alginate.

- 5 Typical ointment bases may be selected from the group comprising beeswax, paraffin, cetanol, cetyl palmitate, vegetable oils, sorbitan esters of fatty acids (Span), polyethylene glycols, and condensation products between sorbitan esters of fatty acids and ethylene oxide, e.g. polyoxyethylene sorbitan monooleate (Tween).
- 10 Typical hydrophobic ointment bases may be selected from the group comprising paraffins, vegetable oils, animal fats, synthetic glycerides, waxes, lanolin, and liquid polyalkylsiloxanes. Typical hydrophilic ointment bases are but not limited to solid macrogols (polyethylene glycols).
- 15 Suitable powder components may be selected from the group comprising alginate, collagen, lactose, powder, which is able to form a gel when applied to a wound (absorbs liquid/wound exudate).

Suitable diluents and disintegrating agents may be selected from the group comprising

- 20 lactose, saccharose, emdex, calcium phosphates, calcium carbonate, calcium sulphate, mannitol, starches and microcrystalline cellulose.

Suitable binding agents may be selected from the group comprising saccharose, sorbitol, gum acacia, sodium alginate, gelatine, starches, cellulose, sodium carboxymethylcellulose,

- 25 methylcellulose, hydroxypropylcellulose, polyvinylpyrrolidone and polyethyleneglycol.

Typical wetting agents may be selected from the group comprising sodium laurylsulphate and polysorbate 80.

- 30 Suitable lubricants may be selected from the group comprising talcum, magnesium stearate, calcium stearate, silicium oxide, precinol and polyethyleneglycol.

Suitable coating agents may be selected from the group comprising

- hydroxypropylcellulose, hydroxypropylmethylcellulose, polyvinylpyrrolidone, ethylcellulose  
35 and polymethylacrylates.

Typical suppository bases may be selected from the group comprising oleum cacao, adeps solidus and polyethyleneglycols.

The present inventor has recognised the therapeutic effect of the complexes and compositions of this invention, partly by observing the reduced inflammation of sub-chronic phorbol ester induced inflamed mouse ear upon administering the complexes and compositions. This test model is a commonly employed method for evaluation of anti-inflammatory drugs for chronic inflammatory conditions.

The acute anti-inflammatory activity was demonstrated in the TPA induced ear inflammation test in mice, which is a commonly employed method for screening and evaluation of antiinflammatory drugs. This model has broad relevance to inflammatory reactions that occur in various hypersensitivity, allergic and autoimmune diseases. Furthermore TPA is known to induce cancer in mice and substances that inhibit TPA induced inflammation thus also inhibit the formation of cancer.

Thus, in a broad sense the chemical complexes or compositions provides an immunomodulating effect. Moreover, the inventor has recognised that a number of diseases or conditions with similarities in the etiology of the inflammatory reactions that are provoked in the sub-chronic phorbol ester induced inflamed mouse ear may be effectively treated by the present complexes and compositions of the invention. Such diseases and conditions relate in general to those associated with hypersensitivity reactions and inflammatory reactions. In a more specific sense, the chemical complexes or compositions of the invention provides suppression of hypersensitivity reactions, suppression of inflammatory reactions, suppression of IgE mediated allergic reactions, suppression of autoimmune reactions, reduction of pain, and suppression of cancer.

Hence, a further aspect of the invention relates to a method for immunomodulation in a mammal, such as a human, comprising the administration to said mammal of an effective amount of a combination of a fatty acid ester of a polyhydroxyalkane and a pyridine carboxy derivative, or a chemical complex comprising a fatty acid ester of a polyhydroxyalkane and a pyridine carboxy derivative.

As used herein, the term "effective amount" relates to the effective dose to be determined by a qualified practitioner, who may titrate dosages to achieve the desired response. Factors for consideration of dose will include potency, bioavailability, desired pharmacokinetic/pharmacodynamic profiles, condition of treatment, patient-related factors (e.g. weight, health, age, etc.), presence of co-administered medications (e.g., anticoagulants), time of administration, or other factors known to a medical practitioner.



As used herein, the term "treatment" relates to treatment of symptoms or prevention the relapse of symptoms in a person diagnosed with a disease related to inflammation, hypersensitivity, infection, cancer and/or pain.

- 5 A still further aspect relates to a method for the treatment of infections or diseases associated with infections selected from the group consisting of microbial infections, viral infections, infections caused by parasites, infections caused by fungi in a mammal, such as a human, comprising the administration to said mammal an effective amount of a combination of a fatty acid ester and a pyridine carboxy derivative as disclosed herein.

10

As stated the complexes and compositions according to the invention may be applicable for the preparation of a medicament. Thus, other aspects of the invention relates to the use of a combination of a fatty acid ester and a pyridine carboxy derivative for the preparation of a medicament for the treatment of infections or diseases associated with infections

- 15 selected from the group consisting of microbial infections, viral infections, infections caused by parasites, infections caused by fungi in a mammal, such as a human.

As recognised by the present inventor, the combination of components as disclosed herein may be used for the treatment of a disease and disorder associated with hypersensitivity

- 20 and/or inflammatory reactions or conditions, such as a disease and a disorder that may be selected from the group consisting of hypersensitivity skin disease, pruritus, urticaria, atopic eczema, contact dermatitis, seborrhoeic dermatitis, acne, rosacea, alopecia, vitiligo, psoriasis IgE mediated allergic reactions, asthma, allergic rhinitis, anaphylaxis, autoimmune disease, chronic inflammatory disease, Crohn's disease, ulcerative colitis, 25 rheumatoid arthritis, gout, osteoarthritis, inflammation associated with pain and inflammation associated with cancer.

For illustrative purposes, the treatment of inflammatory conditions relates to the treatment of Autoimmune hepatitis, Primary biliary cirrhosis, Primary sclerosing cholangitis,

- 30 Autoimmune hemolytic anemias, Grave's disease, Myasthenia gravis, Type 1 Diabetes Mellitus, Inflammatory myopathies, Multiple sclerosis, Hashimoto's thyroiditis, Autoimmune adrenalitis, Crohn's Disease, Ulcerative Colitis, Glomerulonephritis, Progressive Systemic Sclerosis (Scleroderma), Sjögren's Disease, Lupus Erythematosus, Primary vasculitis, Rheumatoid Arthritis, Juvenile Arthritis, Mixed Connective Tissue 35 Disease, Psoriasis, Pemfigus, Pemfigoid, and Dermatitis Herpetiformis.

The therapeutic action of the complexes and compositions of the invention may be relevant to diseases associated with hypersensitivity reactions or inflammation in general.

Particularly, the treatment of hypersensitivity relates to the treatment of infections (viral, bacterial, fungal, parasitic), cold and flu, contact dermatitis, insect bites, allergic vasculitis, post-operative reactions, transplantation rejection (graft-versus-host disease), and so forth.

5

Treatment of IgE mediated allergic reaction or condition relates to the treatment of asthma, eczema (e.g. atopic dermatitis), urticaria, allergic rhinitis and anaphylaxis.

Accordingly, the complexes or compositions of the invention are particularly suitable for the treatment of inflammatory skin diseases associated with secondary infections, e.g. seborrhoeic dermatitis, atopic dermatitis, acne, rosacea, psoriasis, etc. Such secondary infections may often occur in association with any inflammatory condition of the skin or mucous membranes.

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Moreover, the chemical complex or composition of the present invention may be used in a method for the treatment or prevention of pain associated with inflammation. The applicant proposes the hypothesis that the therapeutic action is related to immunomodulation, possibly to a suppressing effect on hypersensitivity reactions.

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As mentioned, a still further aspect of the invention relates to the treatment of the treatment of infections or diseases associated with infections selected from the group consisting of microbial infections, viral infections, infections caused by parasites, infections caused by fungi in a mammal, comprising administration of the combination of components as disclosed herein. A broad spectrum of antibacterial, antifungal, antiviral and antiparasital effects can be anticipated.

In one aspect the invention relates to the treatment of bacterial infections or diseases associated with bacterial infections in a mammal. Relevant but non-limiting examples of target organisms include: gram positive bacteria e.g. *Bacillus subtilis*, *Brevibacterium ammoniagenes*, *Corynebacterium minutissimum*, *Enterococcus faecalis*, *Enterococcus faecalis*, *Micrococcus luteus*, *Mycobacterium phlei*, *Mycobacterium ranae*, *Staphylococcus aureus*, , *Staphylococcus aureus* (Methicillin Resistant), *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Streptococcus faecalis*, *Streptococcus mutans*, *Streptococcus pneumoniae*,, *Streptococcus pneumoniae*; gram negative bacteria e.g. *Enterobacter cloacae*, *Escherichia coli*, *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus vulgaris*, *Pseudomonas aeruginosa*, *Salmonella typhimurium*, *Serratia marcescens*; anaerobes e.g. *Actinomyces viscosus*, *Bacteroides fragilis*, *Clostridium sporogenes*, *Corynebacterium acnes*, *Helicobacter pylori*; fungi e.g. *Aspergillus fumigatus*, *Candida albicans*, *Candida*

glabrata, *Cryptococcus neoformans*, *Epidermophyton floccosum*, *Exophiala jeanselmei*, *Microsporum canis*, *Microsporum gypseum*, *Trichophyton mentagrophytes*, *Trichophyton rubrum*, *Aspergillus niger*, *Cladosporium argillaceum*, *Mucor hiemalis*, *Mucor pusillus*, *Paecilomyces varioti*, *Penicillium chrysogenum*, *Penicillium citrinum*, *Pityrosporum ovale*,  
5 *Rhizopus nigricans* and *Saccharomyces cerevisiae*.

Thus, in some embodiments, the treatment, alleviation or prevention of infection with gram positive bacteria or a disease associated with infection with gram positive bacteria may be selected from the group consisting of *Bacillus subtilis*, *Brevibacterium*  
10 *ammoniogenes*, *Corynebacterium minutissimum*, *Enterococcus faecalis*, *Enterococcus faecalis*, *Micrococcus luteus*, *Mycobacterium phlei*, *Mycobacterium ranae*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Streptococcus faecalis*, *Streptococcus mutans* and *Streptococcus pneumoniae* and the treatment, alleviation or prevention of infection with  
15 gram positive bacteria or a disease associated with infection with gram negative or anaerobe bacteria may be selected from the group consisting of *Enterobacter cloacae*, *Escherichia coli*, *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus vulgaris*, *Pseudomonas aeruginosa*, *Salmonella typhimurium*, *Serratia marcescens*, *Actinomyces viscosus*, *Bacteroides fragilis*, *Clostridium sporogenes*, *Corynebacterium acnes* and *Helicobacter pylori*.

20

The combination of a fatty acid ester of formula I and a pyridine carboxy derivative of formula II may be useful in the treatment of fungal infections or diseases associated with fungal infections in a mammal such as for the treatment, alleviation or prevention of infection with fungi or a disease associated with infection with fungi that may be selected  
25 from the group consisting of *Aspergillus fumigatus*, *Candida albicans*, *Candida glabrata*, *Cryptococcus neoformans*, *Epidermophyton floccosum*, *Exophiala jeanselmei*, *Microsporum canis*, *Microsporum gypseum*, *Trichophyton mentagrophytes*, *Trichophyton rubrum*, *Aspergillus niger*, *Cladosporium argillaceum*, *Mucor hiemalis*, *Mucor pusillus*, *Paecilomyces varioti*, *Penicillium chrysogenum*, *Penicillium citrinum*, *Pityrosporum ovale*, *Rhizopus*  
30 *nigricans* and *Saccharomyces cerevisiae*.

The therapeutic action of the complexes of the invention may also be relevant to all known or unknown viral infections or diseases caused by viruses, including both RNA and DNA viruses. Viruses of particular relevance to the present invention include herpesviruses,  
35 adenoviruses, papovaviruses, parvoviruses, picornaviruses, reoviruses, togaviruses, bunyaviruses, orthomyxoviruses, paramyxoviruses, rhabdoviruses, retroviruses, arenaviruses, poxviruses, hepadnaviruses, caliciviruses, flaviviruses, coronaviruses, filoviruses or orthomyxoviruses. Thus, the invention preferably provides a method as described above for the treatment or prevention of infection with herpesviruses,

adenoviruses, papovaviruses, parvoviruses, picornaviruses, reoviruses, togaviruses, bunyaviruses, orthomyxoviruses, paramyxoviruses, rhabdoviruses, retroviruses, arenaviruses, poxviruses, hepadnaviruses, caliciviruses, flaviviruses, coronaviruses, filoviruses or orthomyxoviruses in an individual.

5

Even more preferred, the invention provides a method as described above for the treatment or prevention of infection with rhinovirus, influenzavirus, hepatitisvirus, herpesvirus or cytomegalovirus in an individual.

- 10 In another preferred embodiment, the present invention also provides a method as described above for the treatment or prevention of common cold, influenza, viral pharyngitis, viral pneumonia, or viral hepatitis in an individual.

Moreover, the chemical complexes or compositions of the invention are suitable for the

- 15 treatment or prevention of diseases caused by inflammation of various tissues, such as the inflammation of the prostate, in particular prostatitis. The complexes and compositions of the invention are also suitable for the treatment or prevention of diseases associated with inflammation, pruritus (itch), erythema or hyperproliferation of the skin especially when topical administration is employed.

20

Furthermore, immunomodulation relates to the treatment of autoimmune disease and/or chronic inflammatory disease, at least in part, for the treatment or prevention of diabetes, Crohn's disease, ulcerative colitis, rheumatoid arthritis, gout or osteoarthritis.

- 25 Still further, the chemical complexes or compositions of the invention may be employed for the treatment or prevention of cancer associated with inflammation of any type and at any stage. The present inventor puts forward the hypothesis that the anticancer effect is due to a combination of immunomodulating and tumour-suppressing effects of the complexes and compositions of the invention.

## EXAMPLES

The following examples describe the preparation of chemical complexes of the present invention.

## 5 General method examples 1-100:

The fatty acid mono- or di-esters of a polyhydroxyalkane and the pyridine carboxy derivative are dissolved in as little solvent as possible. The solvent is removed by spray drying or freeze-drying. After the solvent is removed the product is a white to yellowish paste or powder.

10 The solvent is water:acetone in any v/v % combination.

The paste or powder is suitable for any type of product e.g. pharmaceutical products, dietary supplements and cosmetic formulations. Non-limiting examples of such products are tablets, capsules, ointments and lotions as described above.

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Examples 1 to 10: Molar ratio fatty acid mono- or di-esters of a polyhydroxyalkane/ pyridine carboxy derivative 1:10000 (mol/mol).

	Fatty acid mono- or di-esters of a polyhydroxyalkane 1 mol.	Pyridine carboxy derivative 10000 mol.
Example 1.	Ethyleneglycyl-1-hexanoate	Niacinamide
Example 2.	Ethyleneglycyl-1-(4-noneoate)	Niacinamide
Example 3.	Glyceryl-1-heptanoate	N2-methyl-niacinamide
Example 4.	Glyceryl-2-(5-ethyl-octanoate)	N2-ethyl-niacinamide
Example 5.	Trimethyleneglycyl-1-dodecanoate-2-dodecanoate	Aminoniacinamide
Example 6.	Trimethyleneglycyl-1-octadecanoate-2-(5,7,9-heptadecatrienoate)	Thioniacinamide
Example 7.	1,2,3,4-butanetetraol-1-undecanoate-3-nonanoate	Aminoniacinamide
Example 8.	1-ol-2,3-butylenglycyl-1-heptandecanoate-2-heptandecanoate	Niacinamide
Example 9.	Propylenglycyl- 2-(3-methyl-decanoate)	N2-methyl-niacinamide
Example 10.	1,2-butylenglycyl-1-hexanoate-2-hexanoate	Niacinamide

20 Examples 11 to 20: Molar ratio Fatty acid mono- or di-esters of a polyhydroxyalkane / pyridine carboxy derivative 1:5000 (mol/mol).

	Fatty acid mono- or di-esters of a	Pyridine carboxy derivative
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	polyhydroxyalkane 1 mol.	5000 mol.
Example 11.	Ethyleneglycyl-1-octanoate	Niacinamide
Example 12.	Ethylenglycyl-1-octanoate-4-(3-ethyl-hexanoate	Thioniacinamide
Example 13.	1,2,3,4-butanetraol-1-hexadecanoate-(4-(2,4-diethyl-8-hexadecenoate)	Thioniacinamide
Example 14.	1,2,3,4-butanetraol-2-eicosatrienoate	Aminoniacinamide
Example 15.	Glycerol-1-decanoate-2-decanoate	Niacinamide
Example 16.	1,4-butylenglycyl-1-octanoate	N2-methyl-niacinamide
Example 17.	1-ol-2,3-butylenglycyl-1-heptadecanoate-2-heptadecanoate	N2-methyl-niacinamide
Example 18.	Propylenglycyl-1-undecanoate-2-undecanoate	Aminoniacinamide
Example 19.	Propylenglycyl-1-(7,10-octadecadienoate)-2-octanoate	Niacinamide
Example 20.	Glycerol-2-(8,11,14-eicosatrienoate)	N2-methyl-niacinamide

Examples 21 to 30: Molar ratio Fatty acid mono- or di-esters of a polyhydroxyalkane /  
5 pyridine carboxy derivative 1:1000 (mol/mol).

	Fatty acid mono- or di-esters of a polyhydroxyalkane 1 mol.	Pyridine carboxy derivative 1000 mol.
Example 21.	Ethylenglycyl-1-decanoate-2-hexanoate	Niacinamide
Example 22.	Ethylenglycyl-1-(4-tetradecenoate)	Niacinamide
Example 23.	Glycerol-1-octanoate-3-undecanoate	N2-methyl-niacinamide
Example 24.	Glycerol-1-(4-nonenoate)- 3-hexanoate	N2-ethyl-niacinamide
Example 25.	Trimethylglycyl-1-octanoate	Aminoniacinamide
Example 26.	Trimethylenglycyl-1-undecanoate	Thioniacinamide
Example 27.	Propylenglycyl-1-hexanoate	Aminoniacinamide
Example 28.	Propylenglycyl- 2-(3-methyl-decanoate)	Niacinamide
Example 29.	1,2-butylenglycyl-2-octanoate	N2-methyl-niacinamide
Example 30.	1,2-butylenglycyl-1-nonanoate-2-octanoate	Niacinamide

Examples 31 to 40: Molar ratio Fatty acid mono- or di-esters of a polyhydroxyalkane/  
pyridine carboxy derivative 1:500(mol/mol).

	Fatty acid mono- or di-esters of a polyhydroxyalkane 1 mol.	Pyridine carboxy derivative 216 mol.
Example 31.	1,3-butylenglycyl-1-decanoate-3-octanoate	Aminoniacinamide

Example 32.	2,3-butylenglycyl-2-dodecanoate	Niacinamide
Example 33.	2,3-butylenglycyl-2-octanoate-3-octanoate	Thioniacinamide
Example 34.	Ethylenglycyl-1-(3,6-octadecadienoate)-2-octanoate	Niacinamide
Example 35.	Ethylenglycyl-1-(8-methyl-3,6-octadecadienoate)	N2-ethyl-niacinamide
Example 36.	Glyceryl-1-(4,6,10-eicosatrienoate)-2-(4,6,10-eicosatrienoate)	Thioniacinamide
Example 37.	Glyceryl-1-(8-octadecenoate)-3-heptanoate	Niacinamide
Example 38.	Trimethylenglycyl-2-(4-methyl-2,8-eicosadienoate)	Niacinamide
Example 39.	Propylenglycyl-1-nonanoate	N2-ethyl-niacinamide
Example 40.	1,2,3,4-butanetraol-1-decanoate	Thioniacinamide

Examples 41 to 50: Molar ratio Fatty acid mono- or di-esters of a polyhydroxyalkane/ pyridine carboxy derivative 1:100 (mol/mol).

	Fatty acid mono- or di-esters of a polyhydroxyalkane 1 mol.	Pyridine carboxy derivative 100 mol,
Example 41.	1,2,3,4-butanetraol-1-hexadecanoate-(4-(2,4-diethyl-8-hexadecenoate)	Niacinamide
Example 42.	1,2,3,4-butanetraol-2-eicosatrienoate	Thioniacinamide
Example 43.	2,3-butylenglycyl-2-hexanoate	N2-methyl-niacinamide
Example 44.	1-ol-2,3-butylenglycyl-1-(4-methyl-hexanoate)	N2-ethyl-niacinamide
Example 45.	1-ol-2,3-butylenglycyl-1-(3-octenoate)	Thioniacinamide
Example 46.	1,4-butylenglycyl-1-dodecanoate	Aminoniacinamide
Example 47.	1,4-butylenglycyl-1-decanoate-4-decanoate	Niacinamide
Example 48.	1,2,3,4-butanetraol-2-(2-methyl-octanoate)	Niacinamide
Example 49.	1,2,3,4-butanetraol-1-hexanoate-2-hexanoate	Aminoniacinamide
Example 50.	Glyceryl-2-(3,5,7-hexadecatrienoate)	Thioniacinamide

5 Examples 51 to 60: Molar ratio Fatty acid mono- or di-esters of a polyhydroxyalkane/ pyridine carboxy derivative 1:14 (mol/mol).

	Fatty acid mono- or di-esters of a polyhydroxyalkane 2 mol.	Pyridine carboxy derivative 7 mol.
Example 51.	Glyceryl-1-octanoate	Niacinamide
Example 52.	Glyceryl-2-octanoate	Niacinamide

Example 53.	Glyceryl-1-heptanoate	Aminoniacinamide
Example 54.	Glyceryl-1-octanoate-2-octanoate	Thioniacinamide
Example 55.	Glyceryl-2-(3,5,7-hexadecatrienoate)	N2-methyl-niacinamide
Example 56.	Glyceryl-1-(3-ethyl-2-methyl-8,10-eicosadienoate)-2-octanoate	Aminoniacinamide
Example 57.	Propylenglycyl-1-(2,4-ethyl-6-tetradecaenoate)-2-(8,12-hexadecaenoate)	Thioniacinamide
Example 58.	1,2-butylenglycyl-1-decanoate	N2-methyl-niacinamide
Example 59.	1,2-butylenglycyl-1-heptadecanoate-2-(4,8-heptadecadienoate)	Niacinamide
Example 60.	1,2-butylenglycyl-1-(8-ethyl-4-methyl-6,16-octadecadienoate)	Thioniacinamide

Examples 61 to 70: Molar ratio Fatty acid mono- or di-esters of a polyhydroxyalkane/ pyridine carboxy derivative 1:1 (mol/mol).

	Fatty acid mono- or di-esters of a polyhydroxyalkane 1 mol,	Pyridine carboxy derivative 1 mol.
Example 61.	Glyceryl-1-(5,8,11,14,17-eicosapentaenoate)	Niacinamide
Example 62.	Propylenglycyl-1-nonanoate-2-decanoate	Thioniacinamide
Example 63.	Trimethylenglycyl-1-octanoate-2-(4-ethyl-decanoate)	N2-methyl-niacinamide
Example 64.	1,3-butylenglycyl-1-undecanoate	N2-ethyl-niacinamide
Example 65.	1,3-butylenglycyl-3-hexanoate	Thioniacinamide
Example 66.	1,3-butylenglycyl-1-octanoate-3-octanoate	Aminoniacinamide
Example 67.	1-ol-2,3-butylenglycyl-1-undecanoate-2-undecanoate	Niacinamide
Example 68.	1-ol-2,3-butylenglycyl-1-(2-ethyl-nonanoate)-2-hexanoate	Thioniacinamide
Example 69.	Glyceryl-2-octanoate	N2-methyl-niacinamide
Example 70.	Glyceryl-1-octanoate-2-octanoate	N2-ethyl-niacinamide

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Examples 71 to 80: Molar ratio Fatty acid mono- or di-esters of a polyhydroxyalkane/ pyridine carboxy derivative 5:1 (mol/mol).

	Fatty acid mono- or di-esters of a polyhydroxyalkane 5 mol.	Pyridine carboxy derivative 1 mol.
Example 71.	1,4-butylenglycyl-1-octanoate-4-heptanoate	Thioniacinamide
Example 72.	2,3-butylenglycyl-2-dodecanoate-3-heptanoate	Aminoniacinamide



Example 73.	1,2,3,4-butanetraol-2-(2-methyl-octanoate)	Niacinamide
Example 74.	1,2,3,4-butanetraol-1-hexanoate-2-hexanoate	Thioniacinamide
Example 75.	1,4-butyleneglycol-1-(6,10,12,18-tetradecantetraenoate)-4-(4,8-dimethyl-6,13-eicosadienoate)	N2-methyl-niacinamide
Example 76.	1,4-butyleneglycol-1-(2-ethyl-octanoate)-4-(4-nonenoate)	N2-ethyl-niacinamide
Example 77.	Glycerol-1-octanoate	Thioniacinamide
Example 78.	Glycerol-1-(5,8,11,14,17-eicosapentaenoate)	Aminoniacinamide
Example 79.	Glycerol-2-(8,11,14-eicosatrienoate)	Niacinamide
Example 80.	1,2,3,4-butanetraol-2-(2-methyl-octanoate)	Niacinamide

Examples 81 to 85: Molar ratio Fatty acid mono- or di-esters of a polyhydroxyalkane / pyridine carboxy derivative 50:1 (mol/mol).

	Fatty acid mono- or di-esters of a polyhydroxyalkane 50 mol.	Pyridine carboxy derivative 1 mol.
Example 81.	Ethyleneglycol-1-octanoate	Thioniacinamide
Example 82.	Ethyleneglycol-1-octanoate-4-(3-ethyl-hexanoate)	Aminoniacinamide
Example 83.	Glycerol-1-octanoate	Niacinamide
Example 84.	Glycerol-1-(5,8,11,14,17-eicosapentaenoate)	Thioniacinamide
Example 85.	Glycerol-2-(8,11,14-eicosatrienoate)	N2-methyl-niacinamide

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Examples 86 to 90: Molar ratio Fatty acid mono- or di-esters of a polyhydroxyalkane / pyridine carboxy derivative 500:1 (mol/mol).

	Fatty acid mono- or di-esters of a polyhydroxyalkane 500 mol.	Pyridine carboxy derivative 1 mol.
Example 86.	Glycerol-2-(8,11,14-eicosatrienoate)	Thioniacinamide
Example 87.	1,2,3,4-butanetraol-2-(2-methyl-octanoate)	Aminoniacinamide
Example 88.	Glycerol-1-octanoate	Niacinamide
Example 89.	Trimethyleneglycol-2-(4-methyl-2,8-eicosadienoate)	Thioniacinamide
Example 90.	Propyleneglycol-1-nonanoate	N2-methyl-niacinamide

Examples 91 to 96: Molar ratio Fatty acid mono- or di-esters of a polyhydroxyalkane / pyridine carboxy derivative 1000:1 (mol/mol).

	Fatty acid mono- or di-esters of a polyhydroxyalkane 1000 mol.	Pyridine carboxy derivative 1 mol.
Example 91.	Glycerol-1-(5,8,11,14,17-eicosapentaenoate)	Thioniacinamide
Example 92.	Propylenglycol-1-(2,4-ethyl-6-tetradecaenoate)-2-(8,12-hexadecaenoate)	Aminoniacinamide
Example 93.	1,2-butylenglycol-1-decanoate	Niacinamide
Example 94.	1,2-butylenglycol-2-octanoate	Thioniacinamide
Example 95.	Glycerol-2-octanoate	N2-methyl-niacinamide
Example 96.	1,4-butylenglycol-1-decanoate-4-decanoate	N2-ethyl-niacinamide

Examples 97 to 100: Molar ratio Fatty acid mono- or di-esters of a polyhydroxyalkane / 5 pyridine carboxy derivative 10000:1 (mol/mol).

	Fatty acid mono- or di-esters of a polyhydroxyalkane 10000 mol.	Pyridine carboxy derivative 1 mol.
Example 97.	Glycerol-2-octanoate	Thioniacinamide
Example 98.	Ethylenglycol-1-decanoate-2-hexanoate	Aminoniacinamide
Example 99.	1-ol-2,3-butylenglycol-1-(2-ethyl-nonanoate)-2-hexanoate	Niacinamide
Example 100.	Glycerol-2-(8,11,14-eicosatrienoate)	Thioniacinamide

#### General method examples 101-110:

A lotion with a quantity of the Fatty acid mono- or di-esters of a polyhydroxyalkane and 10 the pyridine carboxy derivative are made.

A lotion of the following composition (w/w) % is made

Water:	60.9%
Complex:	5.0%
15 Methylparabene:	0.1%
Tefose 63 (Gattefossé):	12.0%
Arachis oil:	10.0%
Isopropylmyristat (16):	10.0%
Sodium stearoyl lactylate:	2.0%

Examples 101 to 103: 100 g lotion containing 5% (w/w) of a complex comprising a fatty acid mono- or di-ester of a polyhydroxyalkane and a pyridine carboxy derivative in a weight ratio of 1:2 (w/w).

	Fatty acid mono- or di-esters of a polyhydroxyalkane 1.665g	Pyridine carboxy derivative 3.335g
Example 101.	Glyceryl-2-octanoate 1.665g	Thioniacinamide 3.335g
Example 102.	Glyceryl-2-(8,11,14-eicosatrienoate) 1.665g	Aminoniacinamide 3.335g
Example 103.	Ethylenglycyl-1-decanoate-2-hexanoate 1.665g	N2-ethyl-niacinamide 3.335g

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Examples 104 to 106: 100 g lotion containing 10% (w/w) of a complex comprising a fatty acid mono- or di-ester of a polyhydroxyalkane and a pyridine carboxy derivative in a weight ratio of 1:2 (w/w).

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	Fatty acid mono- or di-esters of a polyhydroxyalkane 3.333g	Pyridine carboxy derivative 6.667g
Example 104.	Glyceryl-1-octanoate-2-octanoate 3.333g	Thioniacinamide 6.667g
Example 105.	Glyceryl-1-(5,8,11,14,17-eicosapentaenoate) 3.333g	Aminoniacinamide 6.667g
Example 106.	Glyceryl-2-(8,11,14-eicosatrienoate) 3.333g	N2-ethyl-niacinamide 6.667g

Examples 107 to 110: 500 g lotion containing 5% (w/w) of a complex comprising a fatty acid mono- or di-ester of a polyhydroxyalkane and a pyridine carboxy derivative in a molar ratio of 2:7 (mol/mol).

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	Fatty acid mono- or di-esters of a polyhydroxyalkane	Pyridine carboxy derivative
Example 107.	Glyceryl-1-octanoate 218.3g/mol	Niacinamide 122.13g/mol

	8.451g	16.549g
Example 108.	Glyceryl-2-octanoate 218.3g/mol 8.451g	Niacinamide 122.13g/mol 14.136g
Example 109.	1,3-butylenglycyl-3-hexanoate 188.27g/mol 7.043g	Aminoniacinamide 137.14g/mol 17.957g
Example 110.	Glyceryl-1-octanoate-2-octanoate 328.5g/mol 10.864g	Thioniacinamide 138.19g/mol 18.779g

**Example 111**

Investigation of a complex according to the invention in a recognized pharmacodynamic  
5 model of acute dermal inflammation.

Objective

The objective of this study was to assess the therapeutic value of combining the two types  
of active entities in the complexes of the invention. This was done by comparing a high  
10 dose, corresponding to  $E_{max}$  (the maximal obtainable effect representing the plateau of the  
dose-response curve) with the individual effects of the molar amount present of each  
component of the complex. If the effect of the complex is higher than the sum of the  
components the effect is synergistic. The animal model chosen was the acute 12-O-  
tetradecanoylphorbol-13-acetate (TPA) induced mouse ear inflammation model (Rao TS et  
15 al. *Inflammation* 1993, **17**(6): 723-41). Ear swelling in this model is strongly correlated  
with mediators that play a crucial role in the pathogenesis of human skin diseases and the  
relative potency of topical steroids is well correlated with their relative potency in humans.  
The positive control used in this study was betamethasone 17-valerate applied as a  
commercial preparation with maximum human dose (Celeston® Cutaneous Solution 0.1%,  
20 Shering-Plough). Betamethasone 17-valerate is one of the strongest topical steroids on the  
market and can only be used for a few weeks at a time due to serious adverse effects.

Test articles and vehicle

The test article is the complex prepared according to example 51 (Compound 51 in the  
following). All substances were obtained from Astion A/S, Denmark.

25

Animals

The study was performed in 40 female BALB/ca mice from M & B A/S, DK-8680 Ry. At  
start of the acclimatisation period the mice were in the weight range of 20 g (+/- 5g).

### Housing

The study took place in an animal room provided with filtered air. The temperature in the room was set at 21 - 23°C and the relative humidity to  $\geq 30\%$ . The room was illuminated to give a cycle of 12 hours light and 12 hours darkness. Light was on from 06.00 till 18.00 h.

5

The animals were housed in Macrolon type III cages (40x25x14 cm), 10 in each cage. The cages were cleaned and the bedding changed at least once a week.

### Bedding

10 The bedding was sawdust (Tapvei 4HV) from Tapvei Oy, 73620 Kortteinen, Finland.

### Diet

A complete pelleted rodent diet "Altromin 1324" from Chr. Petersen, DK- 4100 Ringsted, was available ad libitum.

15

### Drinking water

The animals had free access to bottles with domestic quality drinking water. The drinking water was changed daily.

### 20 Animal randomisation and allocation

On the day of arrival the animals were randomly allocated to groups of 10 mice.

### Body weight

The animals were weighed on the day of dosing and termination of the study.

25

### Procedure

The test substances were administered 20 minutes before and 20 minutes after application of TPA to the ear.

30 All groups were treated with 20µl TPA solution 400 µg/ml in acetone, on the right ear.

The groups (n=10) and doses were as follows:

Group	Drug	Dose
1	Vehicle	-
2	Niacinamide	64.1 µmol/ear
3	<i>Rac</i> -1-glycerol-monocaprylate	4.58 µmol/ear
4	Compound 51	4.58 µmol/ear

5	Betamethasone 17-valerate	0.02 mg/ear
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Three hours after the TPA application the mice were sacrificed, the ears cut from the tip with a punch biopsy knife (8 mm diameter) and weighed.

5 Mean weights and standard deviations were calculated. Relative ear oedema was assessed as the weight difference between right and left ear of each mouse expressed as percent of the left ear. Percent inhibition of the relative ear oedema compared with the vehicle treated groups was calculated for the test substance and positive control treated group.

#### 10 Clinical signs

All visible signs of ill health and any behavioural changes were recorded daily during the study. Any deviation from normal was recorded with respect to time of onset, duration and intensity.

#### 15 Statistics

Differences in relative ear oedema between the vehicle treated group and the other groups were tested for significance employing a non-parametric statistical method of analysis, the Mann-Whitney U test. The required level of significance was  $p < 0.05$ .

All statistical analysis was performed employing the statistical software package Analyse-it

20 v. 1.62.

### RESULTS

#### Clinical signs

25 TPA caused an inflammation in the right ears, which was visible after about 30 minutes. It could clearly be observed that the right ears were bright red and the left ears pale. The test articles to some extent prevented the reaction in the right ear. No adverse reactions to Compound 51 or the groups treated with its components were observed.

30

#### Ear oedema

The various concentrations of the test articles inhibited the relative oedema as shown in the table below:

35

Drug	Dose	% Inhibition of relative ear	Mann-Whitney U test
------	------	------------------------------	---------------------

		oedema	
Vehicle	-	-	-
Niacinamide	64.1 $\mu$ mol/ear	18	p=0.0952
Rac-1-glyceril-monocaprylate	4.58 $\mu$ mol/ear	22	P=0.0526
Compound 51	4.58 $\mu$ mol/ear	66	P<0.001
Betamethasone 17-valerate	0.02 mg/ear	66	P<0.001

### CONCLUSION

Compound 51 yielded a statistically significant and dose dependent inhibition of ear oedema comparable to the effect of betamethasone 17-valerate, which was applied at the maximal human clinical dose. This level of efficacy for compound 51 is convincing, since betamethasone 17-valerate is one of the strongest topical steroids on the market. Furthermore, the result indicates a significant synergistic effect of the complex of the invention, since the antiinflammatory effect was 65% higher than the additive effect of the individual active components of the complex. This finding is very surprising and explains how it is possible to obtain an antiinflammatory effect comparable to a strong steroid with substances that are virtually non-toxic and do not induce any of the damaging effects to the skin caused by corticosteroids like betamethasone 17-valerate.

### 15 **Example 112**

Investigation of two complexes according to the invention in a recognized pharmacodynamic model of sub-chronic inflammation.

#### Objective

20 The objective of this study was to assess the therapeutic value of the complexes of the invention in a very demanding pharmacodynamic model of dermal inflammation. Repeated application of TPA to the ears of the mice within 48 hours yields an inflammatory lesion with infiltration of leukocytes and persistent swelling. The reapplication of TPA (8mg/ear) after 48 hours produces an inflammation and ear oedema, which is more dramatic due to the involvement and activation of a vast number of inflammatory cells. Therefore the model is suitable for drug evaluation in relation to more aggravated or chronic inflammatory conditions. The test substance for evaluation is co-applied with the second TPA application. Specifically, the inventor has observed that mild steroids like hydrocortisone have no effect in this model, while only strong steroids have a more significant effect, reflecting the requirements for success in the clinical situation (Stanley

PL et al.: Mouse skin inflammation induced by multiple topical applications of 12-O-tetradecanoylphorbol-13-acetate. Skin Pharmacology 1991, 4: 262-71).

#### Test articles and vehicle

- 5 The test articles are the complexes prepared according to example 51 (Compound 51 in the following) and example 107 (Compound 107 in the following). All substances were obtained from Astion A/S, Denmark.

#### Animals

- 10 The study was performed in 80 female BALB/ca mice from M & B A/S, DK-8680 Ry. At start of the acclimatisation period the mice were in the weight range of 20 g (+/- 5g).

#### Housing

- The study took place in an animal room provided with filtered air. The temperature in the  
15 room was set at 21 - 23°C and the relative humidity to ≥30%. The room was illuminated to give a cycle of 12 hours light and 12 hours darkness. Light was on from 06.00 till 18.00 h.

The animals were housed in Macrolon type III cages (40x25x14 cm), 10 in each cage. The cages were cleaned and the bedding changed at least once a week.

20

#### Bedding

The bedding was sawdust (Tapvei 4HV) from Tapvei Oy, 73620 Kortteinen, Finland.

#### Diet

- 25 A complete pelleted rodent diet "Altromin 1324" from Chr. Petersen, DK- 4100 Ringsted, was available ad libitum.

#### Drinking water

- The animals had free access to bottles with domestic quality drinking water. The drinking  
30 water was changed daily.

#### Animal randomisation and allocation

On the day of arrival the animals were randomly allocated to groups of 10 mice.

- 35 Body weight

The animals were weighed on the day of dosing and termination of the study.

#### Procedure

All groups were treated with 20µl TPA solution 400 µg/ml in acetone, on the right ear.



48 hours later. The test substances were administered 20 minutes before and 20 minutes after re-application of TPA to the ear (20µl TPA solution 400 µg/ml in acetone, on the right ear).

5 The groups (n=10) and doses were as follows:

Group	Drug	Dose
1	Vehicle	-
2	Compound 51	0.5 mg/ear
3	Compound 51	1.0 mg/ear
4	Compound 51	2.0 mg/ear
5	Compound 107	0.5 mg/ear
6	Compound 107	0.1 mg/ear
7	Compound 107	2.0 mg/ear
8	Betamethasone 17-valerate	0.02 mg/ear

Three hours after the TPA application the mice were sacrificed, the ears cut from the tip with a punch biopsy knife (8 mm diameter) and weighed.

10

Mean weights and standard deviations were calculated. Relative ear oedema was assessed as the weight difference between right and left ear of each mouse expressed as percent of the left ear. Percent inhibition of the relative ear oedema compared with the vehicle treated groups was calculated for the test substance and positive control treated group.

15

#### Clinical signs

All visible signs of ill health and any behavioural changes were recorded daily during the study. Any deviation from normal was recorded with respect to time of onset, duration and intensity.

20

#### Statistics

Differences in relative ear oedema between the vehicle treated group and the other groups were tested for significance employing a non-parametric statistical method of analysis, the Mann-Whitney U test. The required level of significance was  $p < 0.05$ .

All statistical analysis was performed employing the statistical software package Analyse-it v. 1.62.

#### RESULTS

Clinical signs

TPA caused an inflammation in the right ears, which was visible after about 30 minutes. It could clearly be observed that the right ears were bright red and the left ears pale. The 5 test articles to some extent prevented the reaction in the right ear. No adverse reactions to Compound 51 or the groups treated with its components were observed.

Ear oedema

The various concentrations of the test articles inhibited the relative oedema as shown in 10 the table below:

Drug	Dose	% Inhibition of relative ear oedema	Mann-Whitney U test
Vehicle	-	-	-
Compound 51	0.5 mg/ear	21	p=0.0753
Compound 51	1.0 mg/ear	26	p=0.0219
Compound 51	2.0 mg/ear	27	p=0.0344
Compound 107	0.5 mg/ear	28	p=0.0159
Compound 107	0.1 mg/ear	30	p=0.0113
Compound 107	2.0 mg/ear	50	P<0.0001
Betamethasone 17-valerate	0.02 mg/ear	31	p=0.0103

CONCLUSION

15

The study demonstrates a dose-dependent and statistically significant effect of both Compound 107 and Compound 51. In the two highest doses Compound 51 reaches a level of efficacy, which is statistically significant and comparable to that of betamethasone 17-valerate, only slightly lower. This is a very noteworthy finding since betamethasone 17-valerate is one of the strongest topical steroids on the market, which may only be used for short periods due to significant adverse effects, while Compound 51 is literally non-toxic and suitable for long-term daily skin treatment or skin care. The study also shows that Compound 107 is comparable to betamethasone 17-valerate at the two lowest doses, but statistically significantly stronger (p=0.0089, Mann-Whitney U test) than betamethasone 17-valerate at the highest dose, yielding over 60% more anti-inflammatory effect than the strong steroid. The results are clinically relevant since all of the tested doses of Compound 107 and Compound 51 may be applied clinically to humans, due to the favourable safety profile.

25

**Example 113****5 Objective**

The objective of this study was to assess the antimicrobial effect of a complex of the invention and the corresponding doses of its components in a number of pathogenic bacteria and fungi.

**10 Test articles and vehicle**

The test articles are the complex prepared according to example 51 (Compound 51 in the following) and its components Glyceryl-1-octanoate and niacinamide. All substances were obtained from Astion A/S, Denmark.

**15 Experimental procedure**

Test substance or vehicle is added to test wells containing the selected microorganisms ( $1 \times 10^4$  to  $5 \times 10^5$  CFU/ml) in cultures grown under controlled conditions. The final inoculum concentration is determined by reference to a standard optical density curve and adjusted as required. After 1 to 4 days, growth of the culture is examined and scored positive (+)

- 20 for inhibition of growth or turbidity, or negative (-) for no effect upon growth or turbidity. An initial test concentration of 3 mM in 1% DMSO is used and dilutions are tested to establish the minimal inhibitory concentration (MIC).

**Results**

- 25 The substances are administered so that the molar concentration of the complex is directly comparable to the molar concentration of the components of the complex.

The following table shows the MIC obtained for each substance:

<b>Organism</b>	<b>Compound 51</b>	<b>Glyceryl-1-octanoate</b>	<b>Niacinamide</b>
Candida albicans	300 $\mu$ M	Not active at tested doses	Not active at tested doses
Epidermophyton floccosum	1000 $\mu$ M	Not active at tested doses	Not active at tested doses
Microsporum canis	1000 $\mu$ M	Not active at tested doses	Not active at tested doses
Streptococcus faecalis	3 mM	Not active at tested doses	Not active at tested doses
Trichophyton rubrum	1000 $\mu$ M	Not active at tested doses	Not active at tested doses

### Conclusion

- The data clearly show that the complexes of the invention are superior to the
- 5 corresponding doses of their individual components, since the complexes displayed clear anti-fungal and anti-bacterial effects, while the components were without effect at the same doses. This clearly demonstrates a synergistic effect of the complex of the invention.

### **Example 114**

10

#### Objective

The objective of this study was to assess the antibacterial effect of a complex of the invention against a methicillin resistant bacteria strain.

#### 15 Test articles and vehicle

The test articles are the complex prepared according to example 51 (Compound 51 in the following). All substances were obtained from Astion A/S, Denmark.

#### Experimental procedure

- 20 Test substance or vehicle is added to test wells containing the selected microorganisms ( $1 \times 10^4$  to  $5 \times 10^5$  CFU/ml) in cultures grown under controlled conditions. The final inoculum concentration is determined by reference to a standard optical density curve and adjusted as required. After 1 to 4 days, growth of the culture is examined and scored positive (+) for inhibition of growth or turbidity, or negative (-) for no effect upon growth or turbidity.
- 25 An initial test concentration of 3 mM in 1% DMSO is used and dilutions are tested to establish the minimal inhibitory concentration (MIC).

### Results

- The substances are administered so that the molar concentration of the complex is directly
- 30 comparable to the molar concentration of the components of the complex.

The following table shows the MIC obtained for each substance:

Organism	Compound 51
Staphylococcus aureus	1000 $\mu$ M
Staphylococcus aureus Methicillin Resistant	300 $\mu$ M

### Conclusion

The data clearly show that the complex of the invention has a convincing inhibiting effect on *Staphylococcus aureus*. Furthermore it is observed that complex is even more effective against the Mithicillin resistant strain, where many existing antibiotics typically show

5 weaker activity against resistant strains.

### **Example 115**

Four human subjects (all male) suffering from moderate to severe seborrhoeic dermatitis in the face were treated with the lotion produced in example 111 for four weeks. All had a  
10 stable disease at the start of treatment and had been suffering from the disease for several years.

One subject experienced a clear improvement of erythema and scaling within 4 days and had an almost cleared face after one week. After two weeks all symptoms were completely gone. Therefore the treatment was stopped and after one week the symptoms had started  
15 to come back. Treatment was reinitiated and after two days all symptoms had gone.

The three other subjects had a very similar experience. They experienced gradual clear improvement during the first two weeks. After three weeks two stopped treatment because they were virtually symptom free. The last subject was symptom free after four weeks.

The two that stopped after three weeks experienced no reoccurrence of symptoms after  
20 four weeks.

### **Example 116**

Two human subjects suffering from moderate persistent acne were treated for 8 weeks with a gel with the following composition (w/w) %:

25	Water:	Ad 100%
	Complex:	5.0%
	Methylparabene:	0.1%
	Carbopol ETD 2020 (Noveon):	0.8.0%
	Potassium hydroxide 10%	ad pH 6.0
30	Propylene glycol:	2.0%
	Glycerol:	2.0%

The complex used in this formulation was the one produced in example 51.

One subject experienced a pronounced improvement during the first week of treatment.

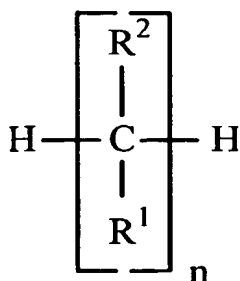
35 This continued and the subject was at least 80% improved after 4 weeks and remained stable until the end of the treatment. The other subject had a slow improvement the first three weeks. Thereafter the improvement was very significant over two weeks. The subject was completely free of symptoms the last three weeks of treatment.

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**CLAIMS**

1. A composition comprising a chemical complex comprising:

5 i) a fatty acid ester of formula I or isomers thereof,

**I**

10

wherein n is 1, 2, 3, 4, 5 or 6;

each R<sup>1</sup> and R<sup>2</sup> is independently selected from the group consisting of H, OH, OM,  
 15 OR', O-CO-R', optionally substituted straight-chain or branched C<sub>1</sub>-C<sub>6</sub> alkyl and optionally substituted straight-chain or branched C<sub>2</sub>-C<sub>6</sub> alkenyl,

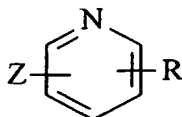
wherein R' is selected from the group consisting of optionally substituted C<sub>6</sub>-C<sub>20</sub> alkyl and optionally substituted C<sub>6</sub>-C<sub>20</sub> alkenyl, and wherein M is an alkali metal;

20

provided that at least one of R<sup>1</sup> and R<sup>2</sup> is a group -O-CO-R' or -OR'; and

ii) a pyridine derivative of formula II or a salt thereof,

25

**II**

wherein R is one substituent selected from the group consisting of -C(=X)R<sub>a</sub>" and -  
 30 CH(R<sub>b</sub>"')XH;

wherein X is O or S,

5  $R_a''$  is selected from the group consisting of H, OH,  $OR'''$ ,  $NH_2$ ,  $NHR'''$ ,  $NR'''R''''$ ,  $CH_2COOH$ ,  $O^-Y^+$  and halogen,

$R_b''$  is selected from the group consisting of H and  $CH_2COOH$ ,

10 wherein  $R'''$  and  $R''''$  are independently selected from H, OH, , optionally substituted  $C_1$ - $C_{20}$  straight-chain, branched or cyclic alkyl, optionally containing one or more multiple bonds, and aryl, and wherein  $Y^+$  is a cation selected from optionally substituted mono-, di-, tri- or tetraalkylammonium ions, ammonium ion, and alkali metal ions,;

15 Z is present 0, 1, 2, 3, or 4 times and selected from the group consisting of hydrogen, halogen,  $NH_2$ , methyl,  $OR'''$  or  $-SH$ .

2. A composition comprising a fatty acid ester of formula I and isomers thereof and a pyridine derivative of formula II or a salt thereof,  
20

wherein formula I, n,  $R^1$ ,  $R^2$ ,  $R'$  M, formula II, R,  $R_a''$ ,  $R_b''X$ ,  $R'''$ ,  $R''''$  and Z are as defined in claim 1.

3. The composition according to claim 1, wherein  $R'$  is selected from unsubstituted  
25 straight-chain or branched  $C_6$ - $C_{14}$  alkyl and  $C_{14}$ - $C_{20}$  alkenyl.

4. The composition according to any one of the preceding claims, wherein n is 1, 2 or 3.

5. The composition according to any one of the preceding claims, wherein at least one of  
30  $R_1$ ,  $R_2$  and  $R_3$  is OH.

6. The composition according to any one of the preceding claims, wherein at most two of  $R_1$ ,  $R_2$  and  $R_3$  is O-CO- $R'$ .

35 7. The composition according to any one of the preceding claims, wherein O-CO- $R'$  is an acyloxy moiety derived from an acid, HO-CO- $R'$ , selected from the group consisting of caproic acid, caprylic acid, capric acid, lauric acid, myristic acid, myristoleic acid, palmitic acid, palmitoleic acid, linoleic acid,  $\alpha$ -linolenic acid or  $\gamma$ -linolenic acid, ricinoleic acid.



8. The composition according to any one of the preceding claims, wherein O-CO-R' is an acyloxy moiety derived from an acid, HO-CO-R', selected from the group consisting of all-*cis*-5,8,11,14,17-eicosapentaenoic acid and docosahexaenoic acids (DHA).
- 5 9. The composition according to any one of the preceding claims, wherein the fatty acid ester is derived from propylene glycol, glycerol, 1,3-butylene glycol, 2,3-butylene glycol or sorbitol.
- 10 10. The composition according to any one of the preceding claims, wherein the pyridine derivative is a pyridine-3-carboxy derivative, i. e. R is located at the 3-position.
11. The composition according to any one of the preceding claims, wherein each R''' and R'''' is independently selected from the group consisting of optionally substituted C<sub>1</sub>-C<sub>10</sub> alkyl and optionally substituted C<sub>2</sub>-C<sub>10</sub> alkenyl.
- 15 12. The composition according to any one of the preceding claims, wherein R<sub>a</sub>'' is OR''', NH<sub>2</sub>, NHR''' or NR'''R'''' wherein R''' and R'''' are independently selected from the group consisting of optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl and optionally substituted C<sub>2</sub>-C<sub>6</sub> alkenyl.
- 20 13. The composition according to claim 9, wherein R''' is selected from optionally substituted C<sub>1</sub>-C<sub>4</sub> alkyl and optionally substituted C<sub>1</sub>-C<sub>4</sub> alkenyl.
14. The composition according to any one of the preceding claims, wherein the pyridine derivative is selected from the group consisting of niacinamide, thioniacinamide, 6-aminoniacinamide, N<sup>2</sup>-methylniacinamide, N<sup>2</sup>-ethylniacinamide, nicotinic acid, 6-methoxy-niacinamide and salts thereof.
- 25 15. The composition according to any one of claims 1 to 13, wherein the pyridine derivative is in the form of a prodrug selected from inosital hexaniacinate.
- 30 16. The composition according to any one of the preceding claims, wherein the pyridine derivative is selected from the group consisting of niacinamide, thioniacinamide, 6-aminoniacinamide, N<sup>2</sup>-methylniacinamide, N<sup>2</sup>-ethylniacinamide and salts thereof.
- 35 17. The composition according to any one of the preceding claims, wherein the pyridine derivative is niacinamide.
18. The composition according to any one of the preceding claims, wherein the components defined by the formulae I and II are present in a molar ratio of between about

1:10000 to 10000:1, preferably about 1:1000 to 1000:1, more preferably of about 1:100 to 100:1, even more preferably of about 1:10 to 10:1, most preferably of about 1:5 to 5:1 or about 1:2 to 2:1.

5 19. The composition according to any one of the preceding claims, comprising racemic, enantiomerically enriched or enantionerically pure 1-glyceryl-monocaprylate and niacinamide.

10 20. A composition according to any one of claims 1, 3 to 18, further comprising one or more excipient(s) or carrier(s) for formulation of a pharmaceutical, a dietary supplement or a cosmetic.

15 21. The composition according to any one of claims 2 to 18, further comprising one or more excipient(s) or carrier(s) for formulation of a pharmaceutical, a dietary supplement or a cosmetic.

22. The composition according to any one of claims 20 or 21 further comprising one or more therapeutically active agents.

20 23. The composition according to any one of claims 20 to 22 formulated as a pharmaceutical for oral, topical, transdermal, or parenteral administration.

24. Use of a composition as defined in any one of claims 1 to 20 as a dietary supplement.

25 25. Use of a composition as defined in any one of claims 1 to 20 as a cosmetic.

26. Use of a composition as defined in any one of claims 1 to 20 for the cosmetic treatment of conditions selected from the group consisting of acne, acne prone skin, irritated skin, dry skin, skin redness, scaly or flaking skin, sunburn.

30

27. Use of a composition as defined in any one of claims 1 to 20 as an antiseptic agent, disinfectant, bacteriostatic agent, bactericidal agent, protective agent, and/or regenerating agent.

35 28. Use of a combination of a fatty acid ester of formula I and a pyridine carboxy derivative of formula II for the preparation of a medicament for the treatment of infections or diseases associated with infections selected from the group consisting of microbial infections, viral infections, infections caused by parasites, infections caused by fungi in a mammal,

wherein formula I,  $n$ ,  $R^1$ ,  $R^2$ ,  $R^1 M$ , formula II,  $R$ ,  $R_a$ ,  $R_b$ ,  $X$ ,  $R'''$ ,  $R''''$  and  $Z$  are as defined in claim 1.

- 5 29. Use of a combination of a fatty acid ester of formula I and a pyridine carboxy derivative of formula II for the preparation of a medicament for the treatment of viral infections or diseases associated with viral infections in a mammal,

10 wherein formula I,  $n$ ,  $R^1$ ,  $R^2$ ,  $R^1 M$ , formula II,  $R$ ,  $R_a$ ,  $R_b$ ,  $X$ ,  $R'''$ ,  $R''''$  and  $Z$  are as defined in claim 1.

30. The use according to claim 29, for the treatment, alleviation or prevention of infection with virus or a disease associated with infection with virus selected from the group consisting of herpesviruses, adenoviruses, papovaviruses, parvoviruses, picornaviruses,  
15 reoviruses, togaviruses, bunyaviruses, orthomyxoviruses, paramyxoviruses, rhabdoviruses, retroviruses, arenaviruses, poxviruses, hepadnaviruses, caliciviruses, flaviviruses, coronaviruses, filoviruses and orthomyxoviruses.

31. The use according to claim 29, for the treatment, alleviation or prevention of infection  
20 with virus or a disease associated with infection with virus selected from the group consisting of rhinovirus, influenzavirus, hepatitisvirus, herpesvirus and cytomegalovirus.

32. The use according to claim 31, for the treatment, alleviation or prevention of common cold or influenza.

25

33. The use according to claim 31 for the treatment, alleviation or prevention of viral pharyngitis.

34. The use according to claim 31 for the treatment, alleviation or prevention of viral  
30 pneumonia in an individual.

35. The use according to claim 31 for the treatment, alleviation or prevention of viral hepatitis in an individual.

- 35 36. Use of a combination of a fatty acid ester of formula I and a pyridine carboxy derivative of formula II for the preparation of a medicament for the treatment of bacterial infections or diseases associated with bacterial infections in a mammal,

wherein formula I,  $n$ ,  $R^1$ ,  $R^2$ ,  $R'$  M, formula II,  $R$ ,  $R_a''$ ,  $R_b''X$ ,  $R'''$ ,  $R''''$  and  $Z$  are as defined in claim 1.

37. The use according to claim 36, for the treatment, alleviation or prevention of infection  
5 with gram positive bacteria or a disease associated with infection with gram positive  
bacteria selected from the group consisting of *Bacillus subtilis*, *Brevibacterium*  
*ammoniogenes*, *Corynebacterium minutissimum*, *Enterococcus faecalis*, *Enterococcus*  
*faecalis*, *Micrococcus luteus*, *Mycobacterium phlei*, *Mycobacterium ranae*, *Staphylococcus*  
*aureus*, *Staphylococcus epidermidis*, *Streptococcus faecalis*, *Streptococcus mutans* and  
10 *Streptococcus pneumoniae*.

38. The use according to claim 36, for the treatment, alleviation or prevention of infection  
with gram positive bacteria or a disease associated with infection with gram negative or  
anaerobe bacteria selected from the group consisting of *Enterobacter cloacae*, *Escherichia*  
15 *coli*, *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus vulgaris*, *Pseudomonas aeruginosa*,  
*Salmonella typhimurium*, *Serratia marcescens*, *Actinomyces viscosus*, *Bacteroides fragilis*,  
*Clostridium sporogenes*, *Corynebacterium acnes* and *Helicobacter pylori*.

39. Use of a combination of a fatty acid ester of formula I and a pyridine carboxy  
20 derivative of formula II for the preparation of a medicament for the treatment of fungal  
infections or diseases associated with fungal infections in a mammal,

wherein formula I,  $n$ ,  $R^1$ ,  $R^2$ ,  $R'$  M, formula II,  $R$ ,  $R_a''$ ,  $R_b''X$ ,  $R'''$ ,  $R''''$  and  $Z$  are as defined in  
claim 1.

25 40. The use according to claim 39, for the treatment, alleviation or prevention of infection  
with fungi or a disease associated with infection with fungi selected from the group  
consisting of *Aspergillus fumigatus*, *Candida albicans*, *Candida glabrata*, *Cryptococcus*  
*neoformans*, *Epidermophyton floccosum*, *Exophiala jeanselmei*, *Microsporum canis*,  
30 *Microsporum gypseum*, *Trichophyton mentagrophytes*, *Trichophyton rubrum*, *Aspergillus*  
*niger*, *Cladosporium argillaceum*, *Mucor hiemalis*, *Mucor pusillus*, *Paecilomyces varioti*,  
*Penicillium chrysogenum*, *Penicillium citrinum*, *Pityrosporum ovale*, *Rhizopus nigricans* and  
*Saccharomyces cerevisiae*.

35 41. Use of a combination of a fatty acid ester of formula I and a pyridine carboxy  
derivative of formula II for the preparation of a medicament for the treatment of a disease  
and disorder associated with hypersensitivity and/or inflammatory reactions,

wherein formula I,  $n$ ,  $R^1$ ,  $R^2$ ,  $R^1 M$ , formula II,  $R$ ,  $R_a''$ ,  $R_b''X$ ,  $R'''$ ,  $R''''$  and  $Z$  are as defined in claim 1.

42. The use according to claim 41, wherein said disease and disorder is selected from the group consisting of hypersensitivity skin disease, pruritus, urticaria, atopic eczema, contact dermatitis, seborrhoeic dermatitis, acne, rosacea, alopecia, vitiligo, psoriasis IgE mediated allergic reactions, asthma, allergic rhinitis, anaphylaxis, autoimmune disease, chronic inflammatory disease, Crohn's disease, ulcerative colitis, rheumatoid arthritis, gout, osteoarthritis, inflammation associated with pain and inflammation associated with cancer.

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43. The use according to any one of claims 28 to 42, wherein the medicament comprises a composition as defined in any one of claims 1 to 23.

44. The use according to any one of claims 28 to 43, wherein the fatty acid ester and the pyridine carboxy derivative are together comprised in a single formulation or are each individually comprised in separate formulations.

45. The use according to any one of claims 28 to 44, wherein the fatty acid ester and pyridine carboxy derivative is administered by means of oral, topical, transdermal, or parenteral administration, or combinations thereof.

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46. The use according to any one of claims 28 to 45, wherein the medicament further comprises one or more therapeutically active agents.

47. The use according to claim 44, wherein the separate formulations are administered in a simultaneous or non-simultaneous manner.

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48. A method for the treatment of infections or diseases associated with infections selected from the group consisting of microbial infections, viral infections, infections caused by parasites, infections caused by fungi in a mammal, including a human, comprising the administration to said mammal an effective amount of a combination of a fatty acid ester of formula I and a pyridine carboxy derivative of formula II,

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wherein formula I,  $n$ ,  $R^1$ ,  $R^2$ ,  $R^1 M$ , formula II,  $R$ ,  $R_a''$ ,  $R_b''X$ ,  $R'''$ ,  $R''''$  and  $Z$  are as defined in claim 1.

35

49. A method for the treatment of viral infections or diseases associated with viral infections in a mammal, including a human, comprising the administration to said mammal

an effective amount of a combination of a fatty acid ester of formula I and a pyridine carboxy derivative of formula II,

wherein formula I,  $n$ ,  $R^1$ ,  $R^2$ ,  $R'$ ,  $M$ , formula II,  $R$ ,  $R_a$ ,  $R_b$ ,  $X$ ,  $R'''$ ,  $R''''$  and  $Z$  are as defined  
5 in claim 1.

50. The method according to claim 49, for the treatment, alleviation or prevention of infection with virus or a disease associated with infection with virus selected from the group consisting of herpesviruses, adenoviruses, papovaviruses, parvoviruses,  
10 picornaviruses, reoviruses, togaviruses, bunyaviruses, orthomyxoviruses, paramyxoviruses, rhabdoviruses, retroviruses, arenaviruses, poxviruses, hepadnaviruses, caliciviruses, flaviviruses, coronaviruses, filoviruses and orthomyxoviruses.

51. The use according to claim 49, for the treatment, alleviation or prevention of infection  
15 with virus or a disease associated with infection with virus selected from the group consisting of rhinovirus, influenza virus, hepatitis virus, herpesvirus and cytomegalovirus.

52. The use according to claim 49, for the treatment, alleviation or prevention of common cold or influenza.  
20

53. The use according to claim 49 for the treatment, alleviation or prevention of viral pharyngitis.

54. The use according to claim 49 for the treatment, alleviation or prevention of viral  
25 pneumonia in an individual.

55. The use according to claim 49 for the treatment, alleviation or prevention of viral hepatitis in an individual.

30 56. A method for the treatment of a disease and disorder associated with hypersensitivity and/or inflammatory reactions, including a human, comprising the administration to said mammal an effective amount of a combination of a fatty acid ester of formula I and a pyridine carboxy derivative of formula II,

35 wherein formula I,  $n$ ,  $R^1$ ,  $R^2$ ,  $R'$ ,  $M$ , formula II,  $R$ ,  $R_a$ ,  $R_b$ ,  $X$ ,  $R'''$ ,  $R''''$  and  $Z$  are as defined in claim 1.

57. The method according to claim 56, wherein said disease and disorder is selected from the group consisting of hypersensitivity skin disease, pruritus, urticaria, atopic eczema,

contact dermatitis, seborrhoeic dermatitis, acne, rosacea, alopecia, vitiligo, psoriasis IgE mediated allergic reactions, asthma, allergic rhinitis, anaphylaxis, autoimmune disease, chronic inflammatory disease, Crohn's disease, ulcerative colitis, rheumatoid arthritis, gout, osteoarthritis, inflammation associated with pain and inflammation associated with  
5 cancer.

58. The method according to any one of claims 48 to 57, wherein the medicament comprises a composition as defined in any one of claims 1 to 23.

10 59. The method according to any one of claims 48 to 58, wherein the fatty acid ester and the pyridine carboxy derivative are together comprised in a single formulation or are each individually comprised in separate formulations.

15 60. The method according to any one of claims 48 to 59, wherein the fatty acid ester and pyridine carboxy derivative is administered by means of oral, topical, transdermal, or parenteral administration, or combinations thereof.

61. The method according to any one of claims 48 to 60, wherein the medicament further comprises one or more therapeutically active agents.

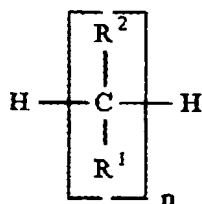
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62. The method according to claim 59, wherein the separate formulations are administered in a simultaneous or non-simultaneous manner.

## AMENDED CLAIMS

[Received by the International Bureau on 01 December 2003 (01.12.03)  
original claims 1, 2, 5, 6, 19, 28, 29, 36, 39, 41, 48, 49 and 56 amended; remaining claims  
unchanged]

1. A composition comprising a chemical complex comprising:
- 5 i) a fatty acid ester in the form of a monoester or in the form of a diester of formula I or isomers thereof,



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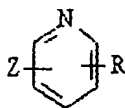
I

wherein n is 1, 2, 3, 4, 5 or 6;

- 15 each  $R^1$  and  $R^2$  is independently selected from the group consisting of H, OH, OM, OR', O-CO-R', optionally substituted straight-chain or branched  $C_1$ - $C_6$  alkyl and optionally substituted straight-chain or branched  $C_2$ - $C_6$  alkenyl,

wherein  $R'$  is selected from the group consisting of optionally substituted  $C_6$ - $C_{20}$   
20 alkyl and optionally substituted  $C_6$ - $C_{20}$  alkenyl, and wherein M is an alkali metal;

- provided that at least one of  $R^1$  and  $R^2$  is a group -O-CO-R' or -OR'; and  
ii) a pyridine derivative of formula II or a salt thereof,



25

II

wherein R is one substituent selected from the group consisting of  $-C(=X)R_b''$  and  $-CH(R_b'')XH$ ;

30

wherein X is O or S,



$R_3''$  is selected from the group consisting of H, OH,  $OR'''$ ,  $NH_2$ ,  $NHR'''$ ,  $NR'''R''''$ ,  $CH_2COOH$ ,  $O^+Y^+$  and halogen,

$R_6''$  is selected from the group consisting of H and  $CH_2COOH$ ,

5

wherein  $R'''$  and  $R''''$  are independently selected from H, OH, , optionally substituted  $C_1$ - $C_{20}$  straight-chain, branched or cyclic alkyl, optionally containing one or more multiple bonds, and aryl, and wherein  $Y^+$  is a cation selected from optionally substituted mono-, di-, tri- or tetraalkylammonium ions, ammonium ion, and alkali metal ions,;

10

Z is present 0, 1, 2, 3, or 4 times and selected from the group consisting of hydrogen, halogen,  $NH_2$ , methyl,  $OR'''$  or  $-SH$ .

- 15 2. A composition comprising a fatty mono-ester or di-ester of formula I and isomers thereof and a pyridine derivative of formula II or a salt thereof,

wherein formula I, n,  $R^1$ ,  $R^2$ ,  $R'$  M, formula II, R,  $R_6''$   $R_6''X$ ,  $R'''$ ,  $R''''$  and Z are as defined in claim 1.

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3. The composition according to claim 1, wherein  $R'$  is selected from unsubstituted straight-chain or branched  $C_6$ - $C_{14}$  alkyl and  $C_{14}$ - $C_{20}$  alkenyl.

4. The composition according to any one of the preceding claims, wherein n is 1, 2 or 3.

25

5. The composition according to any one of the preceding claims, wherein at least one of  $R_1$  and  $R_2$  is OH.

6. The composition according to any one of the preceding claims, wherein at most two of  $R_1$  and  $R_2$  is  $O-CO-R'$ .

30

7. The composition according to any one of the preceding claims, wherein  $O-CO-R'$  is an acyloxy moiety derived from an acid,  $HO-CO-R'$ , selected from the group consisting of caproic acid, caprylic acid, capric acid, lauric acid, myristic acid, myristoleic acid, palmitic acid, palmitoleic acid, linoleic acid,  $\alpha$ -linolenic acid or  $\gamma$ -linolenic acid, ricinoleic acid.

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8. The composition according to any one of the preceding claims, wherein  $O-CO-R'$  is an acyloxy moiety derived from an acid,  $HO-CO-R'$ , selected from the group consisting of all-*cis*-5,8,11,14,17-eicosapentaenoic acid and docosahexaenoic acids (DHA).

40

9. The composition according to any one of the preceding claims, wherein the fatty acid ester is derived from propylene glycol, glycerol, 1,3-butylene glycol, 2,3-butylene glycol or sorbitol.

10. The composition according to any one of the preceding claims, wherein the pyridine derivative is a pyridine-3-carboxy derivative, i. e. R is located at the 3-position.
11. The composition according to any one of the preceding claims, wherein each R''' and R'''' is independently selected from the group consisting of optionally substituted C<sub>1</sub>-C<sub>10</sub> alkyl and optionally substituted C<sub>2</sub>-C<sub>10</sub> alkenyl.
12. The composition according to any one of the preceding claims, wherein R<sub>9</sub>'' is OR''', NH<sub>2</sub>, NHR''' or NR'''R'''' wherein R''' and R'''' are independently selected from the group consisting of optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl and optionally substituted C<sub>2</sub>-C<sub>6</sub> alkenyl.
13. The composition according to claim 9, wherein R''' is selected from optionally substituted C<sub>1</sub>-C<sub>4</sub> alkyl and optionally substituted C<sub>1</sub>-C<sub>4</sub> alkenyl.
14. The composition according to any one of the preceding claims, wherein the pyridine derivative is selected from the group consisting of niacinamide, thioniacinamide, 6-aminoniacinamide, N<sup>2</sup>-methylniacinamide, N<sup>2</sup>-ethylniacinamide, nicotinic acid, 6-methoxy-niacinamide and salts thereof.
15. The composition according to any one of claims 1 to 13, wherein the pyridine derivative is in the form of a prodrug selected from inositol hexaniacinate.
16. The composition according to any one of the preceding claims, wherein the pyridine derivative is selected from the group consisting of niacinamide, thioniacinamide, 6-aminoniacinamide, N<sup>2</sup>-methylniacinamide, N<sup>2</sup>-ethylniacinamide and salts thereof.
17. The composition according to any one of the preceding claims, wherein the pyridine derivative is niacinamide.
18. The composition according to any one of the preceding claims, wherein the components defined by the formulae I and II are present in a molar ratio of between about 1:10000 to 10000:1, preferably about 1:1000 to 1000:1, more preferably of about 1:100 to 100:1, even more preferably of about 1:10 to 10:1, most preferably of about 1:5 to 5:1 or about 1:2 to 2:1.
19. The composition according to any one of the preceding claims, comprising racemic, enantiomerically enriched or enantiomerically pure 1-glyceryl-monocaprylate and niacinamide.
20. A composition according to any one of claims 1, 3 to 18, further comprising one or more excipient(s) or carrier(s) for formulation of a pharmaceutical, a dietary supplement or a cosmetic.

21. The composition according to any one of claims 2 to 18, further comprising one or more excipient(s) or carrier(s) for formulation of a pharmaceutical, a dietary supplement or a cosmetic.
- 5 22. The composition according to any one of claims 20 or 21 further comprising one or more therapeutically active agents.
23. The composition according to any one of claims 20 to 22 formulated as a pharmaceutical for oral, topical, transdermal, or parenteral administration.
- 10 24. Use of a composition as defined in any one of claims 1 to 20 as a dietary supplement.
25. Use of a composition as defined in any one of claims 1 to 20 as a cosmetic.
- 15 26. Use of a composition as defined in any one of claims 1 to 20 for the cosmetic treatment of conditions selected from the group consisting of acne, acne prone skin, irritated skin, dry skin, skin redness, scaly or flaking skin, sunburn.
27. Use of a composition as defined in any one of claims 1 to 20 as an antiseptic agent, disinfectant, bacteriostatic agent, bactericidal agent, protective agent, and/or regenerating agent.
- 20 28. Use of a combination of a fatty mono-ester or di-ester of formula I and a pyridine carboxy derivative of formula II for the preparation of a medicament for the treatment of infections or diseases associated with infections selected from the group consisting of microbial infections, viral infections, infections caused by parasites, infections caused by fungi in a mammal,
- wherein formula I,  $n$ ,  $R^1$ ,  $R^2$ ,  $R'$ ,  $M$ , formula II,  $R$ ,  $R_a$ ,  $R_b$ ,  $X$ ,  $R'''$ ,  $R''''$  and  $Z$  are as defined in claim 1.
- 30 29. Use of a combination of a fatty mono-ester or di-ester of formula I and a pyridine carboxy derivative of formula II for the preparation of a medicament for the treatment of viral infections or diseases associated with viral infections in a mammal,
- 35 wherein formula I,  $n$ ,  $R^1$ ,  $R^2$ ,  $R'$ ,  $M$ , formula II,  $R$ ,  $R_a$ ,  $R_b$ ,  $X$ ,  $R'''$ ,  $R''''$  and  $Z$  are as defined in claim 1.
30. The use according to claim 29, for the treatment, alleviation or prevention of infection with virus or a disease associated with infection with virus selected from the group consisting of herpesviruses, adenoviruses, papovaviruses, parvoviruses, picornaviruses, reoviruses, togaviruses, bunyaviruses, orthomyxoviruses, paramyxoviruses, rhabdoviruses, retroviruses, arenaviruses, poxviruses, hepadnaviruses, caliciviruses, flaviviruses, coronaviruses, filoviruses and orthomyxoviruses.
- 40

31. The use according to claim 29, for the treatment, alleviation or prevention of infection with virus or a disease associated with infection with virus selected from the group consisting of rhinovirus, influenza virus, hepatitis virus, herpes virus and cytomegalovirus.
- 5
32. The use according to claim 31, for the treatment, alleviation or prevention of common cold or influenza.
33. The use according to claim 31 for the treatment, alleviation or prevention of viral
- 10 pharyngitis.
34. The use according to claim 31 for the treatment, alleviation or prevention of viral pneumonia in an individual.
- 15 35. The use according to claim 31 for the treatment, alleviation or prevention of viral hepatitis in an individual.
36. Use of a combination of a fatty mono-ester or di-ester of formula I and a pyridine carboxy derivative of formula II for the preparation of a medicament for the treatment of
- 20 bacterial infections or diseases associated with bacterial infections in a mammal,
- wherein formula I, n, R<sup>1</sup>, R<sup>2</sup>, R' M, formula II, R, R<sub>a</sub>", R<sub>b</sub>"X, R"', R'''' and Z are as defined in claim 1.
- 25 37. The use according to claim 36, for the treatment, alleviation or prevention of infection with gram positive bacteria or a disease associated with infection with gram positive bacteria selected from the group consisting of *Bacillus subtilis*, *Brevibacterium ammoniagenes*, *Corynebacterium minutissimum*, *Enterococcus faecalis*, *Enterococcus faecalis*, *Micrococcus luteus*, *Mycobacterium phlei*, *Mycobacterium ranae*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Streptococcus faecalis*, *Streptococcus mutans* and
- 30 *Streptococcus pneumoniae*.
38. The use according to claim 36, for the treatment, alleviation or prevention of infection with gram positive bacteria or a disease associated with infection with gram negative or
- 35 anaerobe bacteria selected from the group consisting of *Enterobacter cloacae*, *Escherichia coli*, *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus vulgaris*, *Pseudomonas aeruginosa*, *Salmonella typhimurium*, *Serratia marcescens*, *Actinomyces viscosus*, *Bacteroides fragilis*, *Clostridium sporogenes*, *Corynebacterium acnes* and *Helicobacter pylori*.
- 40 39. Use of a combination of a fatty mono-ester or di-ester of formula I and a pyridine carboxy derivative of formula II for the preparation of a medicament for the treatment of fungal infections or diseases associated with fungal infections in a mammal,

wherein formula I,  $n$ ,  $R^1$ ,  $R^2$ ,  $R'$ ,  $M$ , formula II,  $R$ ,  $R_a$ ,  $R_b$ ,  $X$ ,  $R'''$ ,  $R''''$  and  $Z$  are as defined in claim 1.

40. The use according to claim 39, for the treatment, alleviation or prevention of infection  
 5 with fungi or a disease associated with infection with fungi selected from the group consisting of *Aspergillus fumigatus*, *Candida albicans*, *Candida glabrata*, *Cryptococcus neoformans*, *Epidermophyton floccosum*, *Exophiala jeanselmei*, *Microsporum canis*, *Microsporum gypseum*, *Trichophyton mentagrophytes*, *Trichophyton rubrum*, *Aspergillus niger*, *Cladosporium argillaceum*, *Mucor hiemalis*, *Mucor pusillus*, *Paecilomyces variotti*,  
 10 *Penicillium chrysogenum*, *Penicillium citrinum*, *Pityrosporum ovale*, *Rhizopus nigricans* and *Saccharomyces cerevisiae*.

41. Use of a combination of a fatty mono-ester or di-ester of formula I and a pyridine carboxy derivative of formula II for the preparation of a medicament for the treatment of a  
 15 disease and disorder associated with hypersensitivity and/or inflammatory reactions,

wherein formula I,  $n$ ,  $R^1$ ,  $R^2$ ,  $R'$ ,  $M$ , formula II,  $R$ ,  $R_a$ ,  $R_b$ ,  $X$ ,  $R'''$ ,  $R''''$  and  $Z$  are as defined in claim 1.

- 20 42. The use according to claim 41, wherein said disease and disorder is selected from the group consisting of hypersensitivity skin disease, pruritus, urticaria, atopic eczema, contact dermatitis, seborrheic dermatitis, acne, rosacea, alopecia, vitiligo, psoriasis IgE mediated allergic reactions, asthma, allergic rhinitis, anaphylaxis, autoimmune disease, chronic inflammatory disease, Crohn's disease, ulcerative colitis, rheumatoid arthritis, gout,  
 25 osteoarthritis, inflammation associated with pain and inflammation associated with cancer.

43. The use according to any one of claims 28 to 42, wherein the medicament comprises a composition as defined in any one of claims 1 to 23.

- 30 44. The use according to any one of claims 28 to 43, wherein the fatty acid ester and the pyridine carboxy derivative are together comprised in a single formulation or are each individually comprised in separate formulations.

45. The use according to any one of claims 28 to 44, wherein the fatty acid ester and  
 35 pyridine carboxy derivative is administered by means of oral, topical, transdermal, or parenteral administration, or combinations thereof.

46. The use according to any one of claims 28 to 45, wherein the medicament further comprises one or more therapeutically active agents.

- 40 47. The use according to claim 44, wherein the separate formulations are administered in a simultaneous or non-simultaneous manner.

48. A method for the treatment of infections or diseases associated with infections selected from the group consisting of microbial infections, viral infections, infections caused by parasites, infections caused by fungi in a mammal, including a human, comprising the administration to said mammal an effective amount of a combination of a fatty mono-ester or di-ester of formula I and a pyridine carboxy derivative of formula II,

wherein formula I,  $n$ ,  $R^1$ ,  $R^2$ ,  $R'$ ,  $M$ , formula II,  $R$ ,  $R_a$ ,  $R_b$ ,  $X$ ,  $R'''$ ,  $R''''$  and  $Z$  are as defined in claim 1.

49. A method for the treatment of viral infections or diseases associated with viral infections in a mammal, including a human, comprising the administration to said mammal an effective amount of a combination of a fatty mono-ester or di-ester of formula I and a pyridine carboxy derivative of formula II,

wherein formula I,  $n$ ,  $R^1$ ,  $R^2$ ,  $R'$ ,  $M$ , formula II,  $R$ ,  $R_a$ ,  $R_b$ ,  $X$ ,  $R'''$ ,  $R''''$  and  $Z$  are as defined in claim 1.

50. The method according to claim 49, for the treatment, alleviation or prevention of infection with virus or a disease associated with infection with virus selected from the group consisting of herpesviruses, adenoviruses, papovaviruses, parvoviruses, picornaviruses, reoviruses, togaviruses, bunyaviruses, orthomyxoviruses, paramyxoviruses, rhabdoviruses, retroviruses, arenaviruses, poxviruses, hepadnaviruses, caliciviruses, flaviviruses, coronaviruses, filoviruses and orthomyxoviruses.

51. The use according to claim 49, for the treatment, alleviation or prevention of infection with virus or a disease associated with infection with virus selected from the group consisting of rhinovirus, Influenzavirus, hepatitisvirus, herpesvirus and cytomegalovirus.

52. The use according to claim 49, for the treatment, alleviation or prevention of common cold or influenza.

53. The use according to claim 49 for the treatment, alleviation or prevention of viral pharyngitis.

54. The use according to claim 49 for the treatment, alleviation or prevention of viral pneumonia in an individual.

55. The use according to claim 49 for the treatment, alleviation or prevention of viral hepatitis in an individual.

56. A method for the treatment of a disease and disorder associated with hypersensitivity and/or inflammatory reactions, including a human, comprising the administration to said mammal an effective amount of a combination of a fatty mono-ester or di-ester of formula I and a pyridine carboxy derivative of formula II,

wherein formula I,  $n$ ,  $R^1$ ,  $R^2$ ,  $R^1 M$ , formula II,  $R$ ,  $R_a$ ,  $R_b$ ,  $X$ ,  $R'''$ ,  $R''''$  and  $Z$  are as defined in claim 1.

- 5 57. The method according to claim 56, wherein said disease and disorder is selected from the group consisting of hypersensitivity skin disease, pruritus, urticaria, atopic eczema, contact dermatitis, seborrhoeic dermatitis, acne, rosacea, alopecia, vitiligo, psoriasis IgE mediated allergic reactions, asthma, allergic rhinitis, anaphylaxis, autoimmune disease, chronic inflammatory disease, Crohn's disease, ulcerative colitis, rheumatoid arthritis, 10 gout, osteoarthritis, inflammation associated with pain and inflammation associated with cancer.

58. The method according to any one of claims 48 to 57, wherein the medicament comprises a composition as defined in any one of claims 1 to 23.

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59. The method according to any one of claims 48 to 58, wherein the fatty acid ester and the pyridine carboxy derivative are together comprised in a single formulation or are each individually comprised in separate formulations.

- 20 60. The method according to any one of claims 48 to 59, wherein the fatty acid ester and pyridine carboxy derivative is administered by means of oral, topical, transdermal, or parenteral administration, or combinations thereof.

61. The method according to any one of claims 48 to 60, wherein the medicament further 25 comprises one or more therapeutically active agents.

62. The method according to claim 59, wherein the separate formulations are administered in a simultaneous or non-simultaneous manner.

## INTERNATIONAL SEARCH REPORT

International Application No.

PCT 03/00423

<b>A. CLASSIFICATION OF SUBJECT MATTER</b> IPC 7 A61K31/765 A61K31/44 A61P31/04 A61P29/00		
According to International Patent Classification (IPC) or to both national classification and IPC		
<b>B. FIELDS SEARCHED</b> Minimum documentation searched (classification system followed by classification symbols) IPC 7 A61K		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used) EPO-Internal, WPI Data, PAJ, BIOSIS, EMBASE		
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 02 05850 A (PITMY INTERNAT N V ; MEYER PETRUS JOHANNES (ZA)) 24 January 2002 (2002-01-24)	1-9, 12, 18, 20, 21, 23, 27-31, 36-40, 43-51, 58-62
Y	claims 1, 12 figure 7 table 8 page 95, paragraph 5.2 ----- -/--	1-62
<input checked="" type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> Patent family members are listed in annex.		
* Special categories of cited documents : *A* document defining the general state of the art which is not considered to be of particular relevance *E* earlier document but published on or after the international filing date *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) *O* document referring to an oral disclosure, use, exhibition or other means *P* document published prior to the international filing date but later than the priority date claimed *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. *&* document member of the same patent family		
Date of the actual completion of the international search		Date of mailing of the international search report
23 September 2003		01/10/2003
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016		Authorized officer  Giacobbe, S.



## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>WO 01 03696 A (SCARISTA LTD ; HORROBIN DAVID F (GB); GOUAILLE CHRISTINA (SE)) 18 January 2001 (2001-01-18)</p> <p>claims 1-96 page 2, line 8 page 5, lines 11,12 page 8, line 19 page 8, line 28 - line 34</p>	1-9,18, 20-24, 46,47, 56-58, 61,62
X	<p>WO 96 34858 A (REDDEN PETER ; SCOTIA HOLDINGS PLC (GB); MANKU MEHAR (GB); PITT ANDREA) 7 November 1996 (1996-11-07)</p>	1-8,10, 14,18, 20,21, 23,24, 41-47, 56-60,62
Y	<p>page 1, paragraph 1 page 2, paragraph 1 page 4, paragraph 2 - page 5, last line page 8, paragraph 2 - paragraph '0005! claims 1-6 abstract</p>	1-62
Y	<p>PATENT ABSTRACTS OF JAPAN vol. 1997, no. 11, 28 November 1997 (1997-11-28) &amp; JP 09 194306 A (EISAI CO LTD), 29 July 1997 (1997-07-29) abstract</p>	1-62
Y	<p>MCCARTY M F ET AL: "NIACINAMIDE THERAPY FOR OSTEOARTHRITIS - DOES IT INHIBIT NITRIC OXIDE SYNTHASE INDUCTION BY INTERLEUKIN-1 IN CHONDROCYTES?" MEDICAL HYPOTHESES, EDEN PRESS, PENRITH, US, vol. 53, no. 4, October 1999 (1999-10), pages 350-360, XP002901806 ISSN: 0306-9877 abstract</p>	1-62
Y	<p>WO 01 74781 A (ASTION DEV APS ; WEIDNER MORTEN SLOTH (DK)) 11 October 2001 (2001-10-11) page 1, line 5 - page 5, line 3 examples 1-135 pages 1-23</p>	1-62
Y	<p>WO 01 74780 A (ASTION DEV APS ; WEIDNER MORTEN SLOTH (DK)) 11 October 2001 (2001-10-11) page 1, line 5 - page 5, line 33 examples 1-28 claims 1-28</p>	1-62
	-/--	

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 465 423 A (RES FOUND MENTAL HYGIENE) 8 January 1992 (1992-01-08) abstract tables 3,7,11-13,16-19 page 15, line 19 - line 27 claim 1	1-62
Y	DE 42 34 188 A (BEIERSDORF AG) 14 April 1994 (1994-04-14) abstract page 4, line 28 - page 5, line 2 page 5, line 35 - line 38 claim 1	1-62
Y	US 5 231 087 A (THORNFELDT CARL R) 27 July 1993 (1993-07-27) claims 1-4,10	1-62
Y	DE 43 37 711 A (BEIERSDORF AG) 11 May 1995 (1995-05-11) abstract claims 1-4	1-62
Y	EP 0 705 605 A (BEIERSDORF AG) 10 April 1996 (1996-04-10) abstract page 2, line 39 - page 3, line 27 claims 1-6	1-62
Y	US 4 002 775 A (KABARA JON J) 11 January 1977 (1977-01-11) column 2, line 1 - line 21 figure 3 column 3, line 50 - line 68 table 7 column 10, line 41 - line 52	1-62
Y	EP 0 573 253 A (UNILEVER PLC ;UNILEVER NV (NL)) 8 December 1993 (1993-12-08) abstract claims 1-15	1-62
Y	KABARA J J: "MEDIUM-CHAIN FATTY ACIDS AND ESTERS AS ANTIMICROBIAL AGENTS" COSMETIC AND DRUG PRESERVATION, XX, XX, 1984, pages 275-304, XP000989750 page 282, paragraph B	1-62
P,Y	WO 02 083058 A (COHEN IRUN R ;MARGALIT RAANAN (IL); SHINITZKY MEIR (IL); YEDA RES) 24 October 2002 (2002-10-24) abstract page 6, line 19 - line 25 page 9, line 10 - line 14 claim 27	1-62

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/DK 03/00423

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
  
Although claims 24-27 and 48-62 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

## INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/SA/2010 03/00423

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 0205850	A	24-01-2002	AU 8358601 A CA 2416512 A1 WO 0205850 A2	30-01-2002 24-01-2002 24-01-2002
WO 0103696	A	18-01-2001	AU 6167800 A BR 0013157 A CA 2377502 A1 CN 1361690 T CZ 20020058 A3 EE 200200021 A EP 1200085 A1 WO 0103696 A1 HU 0202342 A2 JP 2003504333 T NO 20020090 A NZ 516101 A SK 332002 A3 TR 200200045 T2 ZA 200200259 A	30-01-2001 02-04-2002 18-01-2001 31-07-2002 12-06-2002 15-04-2003 02-05-2002 18-01-2001 28-11-2002 04-02-2003 08-01-2002 30-06-2003 03-12-2002 21-05-2002 22-10-2002
WO 9634858	A	07-11-1996	AT 224353 T AU 713858 B2 AU 5507996 A AU 707600 B2 AU 5508096 A AU 713045 B2 AU 5508196 A BG 63892 B1 BG 102011 A BG 102012 A BR 9606604 A BR 9606607 A CA 2218699 A1 CA 2218702 A1 CA 2220091 A1 CZ 9703413 A3 CZ 9703414 A3 DE 69623764 D1 DE 69623764 T2 DK 823889 T3 EE 9700275 A EE 9700281 A EP 0823895 A1 EP 0823889 A1 EP 0823897 A1 ES 2185772 T3 WO 9634855 A1 WO 9634846 A1 WO 9634858 A1 HU 9802308 A2 HU 9802384 A2 IL 118061 A JP 11504339 T JP 11504914 T JP 11504340 T NO 975035 A NO 975036 A NZ 306508 A	15-10-2002 09-12-1999 21-11-1996 15-07-1999 21-11-1996 25-11-1999 21-11-1996 30-05-2003 29-05-1998 29-05-1998 16-09-1997 15-12-1998 07-11-1996 07-11-1996 07-11-1996 15-07-1998 12-08-1998 24-10-2002 28-05-2003 27-01-2003 15-04-1998 15-04-1998 18-02-1998 18-02-1998 18-02-1998 01-05-2003 07-11-1996 07-11-1996 07-11-1996 01-02-1999 29-03-1999 23-05-2002 20-04-1999 11-05-1999 20-04-1999 22-12-1997 17-12-1997 26-01-2001

## INTERNATIONAL SEARCH REPORT

Information on patent family members

Internal Application No

PCT 03/00423

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9634858	A		NZ 306509 A	29-06-1999
			NZ 306510 A	28-05-1999
			PL 323152 A1	16-03-1998
			PL 323176 A1	16-03-1998
			PT 823889 T	28-02-2003
			SI 823889 T1	30-04-2003
			SK 146997 A3	07-10-1998
			SK 147097 A3	03-06-1998
			TR 9701276 T1	21-02-1998
			TR 9701277 T1	21-02-1998
			US 6245811 B1	12-06-2001
			US 6555700 B1	29-04-2003
JP 09194306	A	29-07-1997	NONE	
WO 0174781	A	11-10-2001	AU 4231501 A	15-10-2001
			WO 0174781 A1	11-10-2001
WO 0174780	A	11-10-2001	AU 4231301 A	15-10-2001
			CA 2403885 A1	11-10-2001
			WO 0174780 A1	11-10-2001
			EP 1268430 A1	02-01-2003
			US 2001027203 A1	04-10-2001
			US 2001036924 A1	01-11-2001
EP 0465423	A	08-01-1992	AU 7924891 A	02-01-1992
			BR 9102672 A	04-02-1992
			CA 2045262 A1	26-12-1991
			EP 0465423 A2	08-01-1992
			FI 912955 A	26-12-1991
			GR 91100276 A ,B	25-08-1992
			IE 912175 A1	01-01-1992
			JP 6040810 A	15-02-1994
			NO 912461 A	27-12-1991
			US 5434182 A	18-07-1995
			US 5466714 A	14-11-1995
			US 5624958 A	29-04-1997
DE 4234188	A	14-04-1994	DE 4234188 A1	14-04-1994
			EP 0592876 A1	20-04-1994
US 5231087	A	27-07-1993	CA 1317884 C	18-05-1993
DE 4337711	A	11-05-1995	DE 4337711 A1	11-05-1995
EP 0705605	A	10-04-1996	DE 4434781 A1	04-04-1996
			EP 0705605 A2	10-04-1996
			JP 8099878 A	16-04-1996
US 4002775	A	11-01-1977	US 4067997 A	10-01-1978
			JP 1179254 C	30-11-1983
			JP 50031034 A	27-03-1975
			JP 57041442 B	03-09-1982
EP 0573253	A	08-12-1993	AT 204455 T	15-09-2001
			AU 668559 B2	09-05-1996
			AU 3989693 A	09-12-1993
			DE 69330625 D1	27-09-2001

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT 03/00423

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0573253 A		DE 69330625 T2	07-03-2002
		EP 0573253 A2	08-12-1993
		ES 2162807 T3	16-01-2002
		JP 7291823 A	07-11-1995
WO 02083058 A	24-10-2002	WO 02083058 A2	24-10-2002